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Some New Routes for the Preparation of 3-Amino-2-phenyl-4(1*H*)-quinolinones from Anthranilamides

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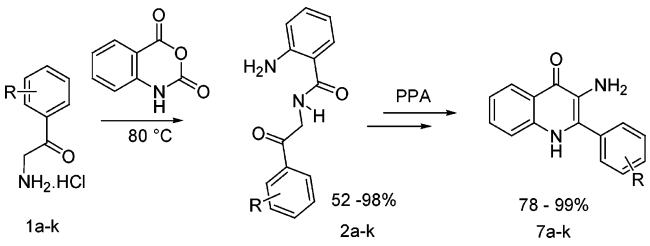

Several new routes for the preparation of 3-amino-2-phenyl-4-1(*H*)-quinolinone **7a** are compared. The most efficient is based on the cyclization of phenacyl anthranilamide **2a** in the presence of (poly)phosphoric acid. The mechanisms of the rearrangements involved are discussed on the basis of the structures of isolated heterocyclic intermediates. The best methodology for the preparation of the title compound **7a** was verified, and 10 other quinolinones **7** were prepared.

The cyclization of *esters* of anthranilic acids and 2-hydroxyketones has been studied for some time. Originally, the formation of a seven-membered ring was described in the literature.[1,2] It was proved later that rearrangement to a six-membered ring takes place leading to a general, simple, and efficient synthetic entry into 2-substituted-3-hydroxy-4(1*H*)-quinolinones.[3−5] These compounds are interesting because they can be considered as isosteres of flavonols, which are well-known for their applications in medicine[6] and for the various kinds of biological activity they exhibit.[7] For this reason, and in an effort to improve the synthesis, the course of the cyclization of anthranilamides **2** under various conditions was studied.

Scheme 1 outlines the reaction conditions and final products. The key intermediate **2a** (and analogues) has been proposed several times in the literature[8,9] but has not been previously isolated. These compounds were prepared by reaction of the commercially available 2-aminoacetophenones **1a**−**k** with isatoic anhydride, following a method similar to that employed for the synthesis of a chloro analogue.[10] Diazepinone **4a** has been prepared, and its melting point is reported in the literature,[8] but we have found that, in contrast to the previous report, use of piperidine as a catalyst led to a less clean reaction.

When anthranilamide **2a** was heated with polyphosphoric acid at 150 °C, we observed the formation of some diazepinone **4a** in TLC and another compound which was identified as aminoquinolone **7a** by NMR, MS, and X-ray diffraction. This compound (**7a**) is known in the literature[11] and was prepared, albeit in very low yield, from 2-phenyl-3-acetyl-4(1*H*)-quinolone in a multistep synthesis. In contrast, the yield of cyclization described here is very high (97%) and **7a** generated by this method is unusually pure (98% purity was determined for the crude product by HPLC). Furthermore, starting materials are readily available. Formation of compound **7a** was also observed after heating of anthranilamide **2a** with phosphoric acid.

The cyclization of anthranilamides **2** in acid conditions is interesting not only from a preparative point of view, but also for mechanistic reasons. Formation of diazepinone **4a** as an intermediate during the reaction was followed by TLC and HPLC. Its concentration remained approximately stable as long as compound **2a** was present in the reaction mixture, being gradually replaced by **7a** when **2a** disappeared. At the end of the reaction, only quinolinone **7a** was present. Heating diazepinone **4a** with phosphoric or polyphosphoric acid also afforded compound **7a**.

The reactivity of anthranilamide **2a** and diazepinone **4a** with different acids and reagents under various conditions was tested (Scheme 1). When **4a** was heated in concentrated hydrochloric acid, anthranilamide **2a** was formed with only traces of aminoquinolinone **7a**. When diazepinone **4a** was heated in sulfuric acid, anthranilamide **2a** was formed and several other compounds appeared in TLC. The main product was the same as that resulting from the reaction of anthranilamide **2a** with sulfuric acid[9,13] and was subsequently identified as the oxazole derivative **3a**, arising from intramolecular dehydration of **2a**. Heating the compound **3a** with polyphosphoric acid at 170 °C caused aminoquinolone **7a** to be formed in very high yield.

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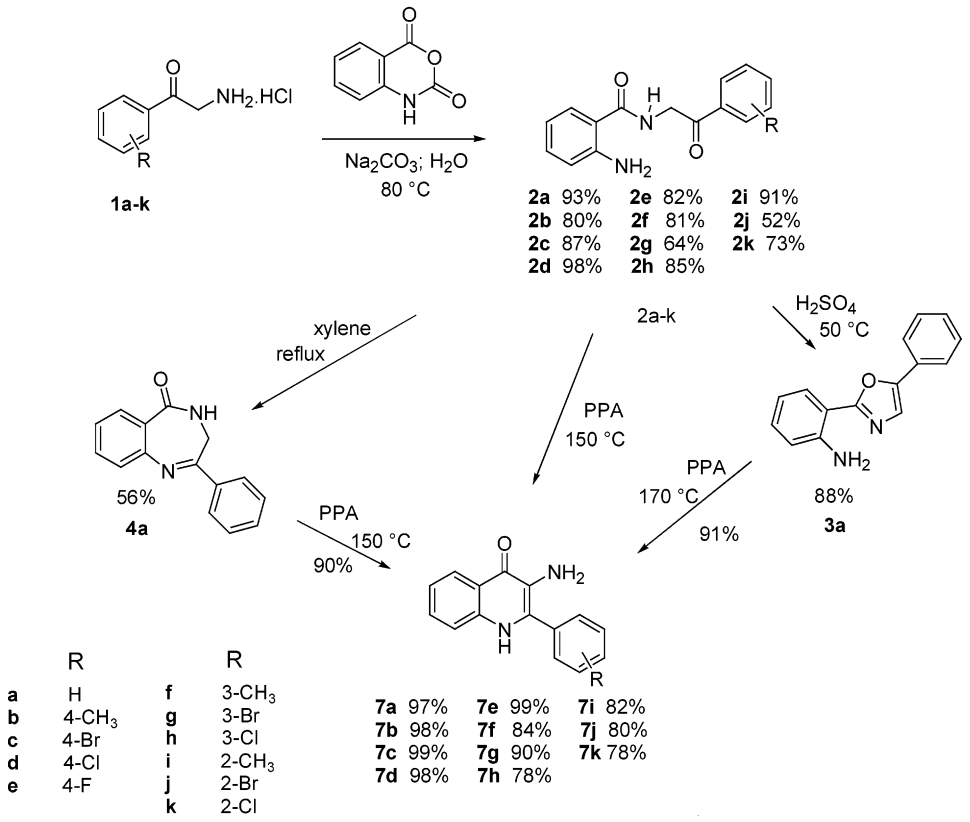
SCHEME 1



Formation of anthranilamide **2a** or diazepinone **4a** was not observed during the reaction, but this is not surprising, as reaction temperatures were very high and these compounds are known to be unstable under such conditions. Other attempted cyclization conditions ($POCl_3$, $SOCl_2$) led to complex mixtures. The most successful method of cyclization of anthranilamide **2a** in polyphosphoric acid was also tested on phenacyl anthranilamide derivatives **2b**−**k**. The aminoquinolones **7b**−**k** resulted in high yield and purity.

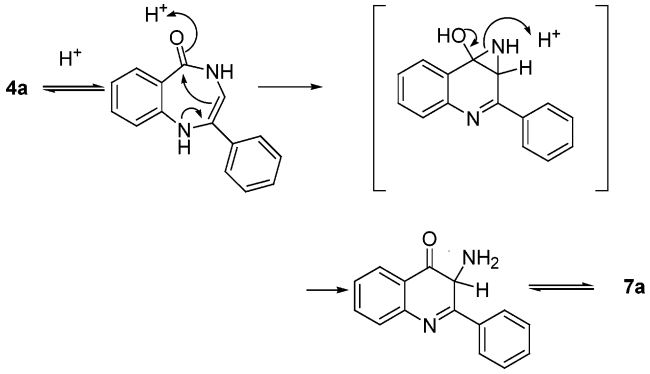
These data suggest that formation of a seven-membered ring occurs initially and is then followed by rearrangement, as shown in Scheme 2. A similar type of rearrangement in the reactions of phenacyl anthranilate was anticipated, but the formation of an intermediate analogous to **4a** was not observed.[3,12]

The behavior of the isomeric anthranilamide **6** with polyphosphoric acid under similar conditions was tested. This reaction provided quinolinone **7a** as the sole identifiable product in 43% isolated yield (Scheme 3).

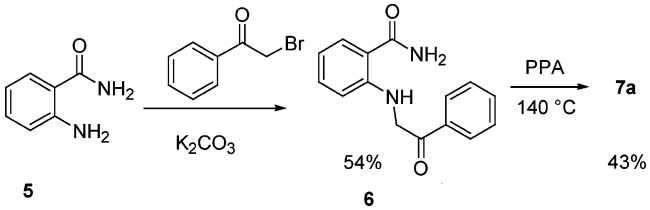
The formation of compound **7a** from compound **6** is tentatively explained in Scheme 4, involving formation of an aziridine intermediate.

In conclusion, the cyclization of anthranilamides **2** constitutes an efficient and straightforward pathway toward derivatives of 3-amino-2-phenyl-4-1(*H*)-quinolinone (**7a)**, compounds with a prospective application in medicine. Starting anthranilamides

SCHEME 2



SCHEME 3



2 were prepared from simply available 2-aminoacetophenones and isatoic anhydride. The mechanism of transformation anthranilamide **2a** and to rearrange intermediate **4a** with a seven-membered ring to the final 3-amino-2-phenyl-4-1(*H*)-quinolinone **7a** was proposed.

Experimental Section

MS characterization was carried out using the direct exposure probe-chemical ionization-tandem mass spectrometry (DEP-CI-MS-

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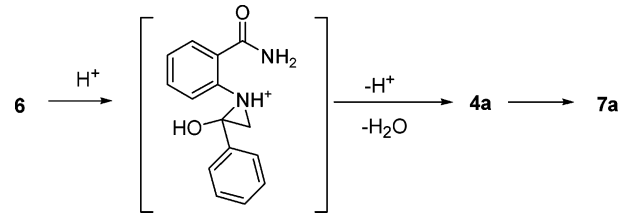
SCHEME 4



MS) technique with quadrupole ion trap mass analyzer and methane as the CI reagent gas. Thin-layer chromatography was performed on Sil G/UV254 plates with UV detection at 254 nm. NMR spectra were measured with a spectrometer operating at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C). The compounds were dissolved in DMSO-d_6 and measured at 300 K. Melting points were determined on a Boetius stage and were not corrected.

2-Amino-*N*-(2-oxo-2-phenylethyl)benzamide (2a). 2-Aminoacetophenone hydrochloride (**1a**) (1 g, 5.83 mmol) was dissolved in water (20 mL). Isatoic anhydride (1.0 g, 6.14 mmol) and sodium carbonate (0.38 g, 3.59 mmol) were added. After being stirred for 5 min, the reaction mixture was gradually heated to 80 °C over 30 min. At 30 °C the mixture began to foam. On reaching 80 °C it was stirred for a further 10 min. After this, the solid phase was filtered off and washed with a solution of sodium carbonate and water to neutral pH. The solid was dried in vacuo to yield 1.38 g (93%) of compound **2a**. The product was used for the next synthetic step without purification, but for analytical purposes it was crystallized: mp 128−130 °C (acetone). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.55 (1H, t, J = 5.5 Hz), 8.06−8.01 (2H, m), 7.68 (1H, tt, J = 7.5, 1.3 Hz), 7.61−7.52 (3H, m), 7.20−7.13 (1H, m), 6.71 (1H, d, J = 8.2 Hz), 6.58−6.51 (1H, m), 6.41 (2H, bs), 4.71 (2H, d, J = 5.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 195.6, 169.1, 149.7, 135.1, 133.4, 131.9, 128.8, 128.1, 127.8, 116.4, 114.6, 114.0, 46.1. IR (KBr, cm^{-1}): 3449, 3344, 3331, 1697, 1633, 1534. CI(methane)-MS; full MS, *m*/*z* (relative intensity) 255 (30) $[M + H]^+$, 283 $[M + C_2H_5]^+$, 295 $[M + C_3H_5]^+$, 237 $[M + H - H_2O]^+$, 120 (100) $[C_6H_4CO(NH_2)]^+$; MS^2(255,w5,EV1), *m*/*z* 237, 235, 224, 194, 149, 120. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.53; H, 5.53; N, 11.00.

2-(5-Phenyl-2-oxazolyl)phenylamine (3a). A mixture of anthranilamide **2a** (280 mg, 1.1 mmol) and sulfuric acid (3 mL) was heated to 50 °C for 3 h, and the reaction mixture was subsequently poured into water and neutralized with sodium carbonate. The precipitated product was filtered off, dried, and crystallized from methanol: 230 mg (88%), mp 130−131.5 °C (lit:[13] mp 128 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.91 (1H, dd, J = 8.1, 1.5 Hz), 7.86−7.82 (3H, m), 7.54−7.47 (2H, m), 7.38 (1H, tt, J = 7.3, 1.3 Hz), 7.24−7.17 (1H, m), 6.93−6.73 (2H, bs), 6.86 (1H, dd, J = 8.3, 0.8 Hz), 6.70−6.64 (1H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7, 148.6, 147.3, 131.3, 129.1, 128.4, 127.4, 127.0, 123.9, 123.1, 115.8, 115.4, 107.5. IR (KBr, cm^{-1}): 3462, 3360, 3339, 1603, 1537, 1489, 1446. CI(methane)-MS; full MS, *m*/*z* (relative intensity) 237 (100) $[M + H]^+$, 265 $[M + C_2H_5]^+$, 277 $[M + C_3H_5]^+$; MS^2(237,w5,EV1.5), *m*/*z* 236, 219, 209, 180, 131. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.20; H, 5.17; N, 11.95.

2-Phenyl-3*H*-benzo[*e*][1,4]diazepin-5-one (4a). Anthranilamide **2a** (0.5 g, 1.97 mmol) was dissolved in xylene (5 mL), and the reaction mixture was heated under reflux for 4 h. The organic solution was evaporated to dryness, and the residue was purified by column chromatography on silica gel with toluene as eluent. One main product was isolated. This product was crystallized from tetrahydrofuran to give compound **4a**: 260 mg (56%), mp 132−135 °C (lit:[8] mp 173−175 °C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.56 (1H, t, J = 5.9 Hz), 8.10−8.06 (2H, m), 7.89−7.84 (1H, m), 7.66−7.51 (4H, m), 7.40−7.32 (2H, m), 3.96 (2H, d, J = 5.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.9, 167.4, 146.4, 136.2, 131.6, 131.3, 129.8, 128.8, 127.8, 126.6, 126.5, 125.6, 38.5. IR (KBr, cm^{-1}): 3436, 1658, 1596, 1466. CI(methane)-MS; full MS, *m*/*z* (relative intensity) 237 (100) $[M + H]^+$, 265 $[M + C_2H_5]^+$, 277 $[M + C_3H_5]^+$; MS^2(237,w5,EV1.5), *m*/*z* 235, 220, 208, 194, 179, 167, 134, 105. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.31; H, 5.14; N, 11.90.

2-(2-Oxo-2-phenylethylamino)benzamide (6). Anthranilamide (**5**) (1 g, 7.3 mmol) was dissolved in dimethylformamide (10 mL), and potassium carbonate (1 g, 7.14 mmol) was added. The reaction mixture was heated to 90 °C and stirred for 2 h. Then the solution was cooled to 20 °C, and phenacyl bromide (1.45 g, 7.3 mmol) was added. After being stirred for 180 min, the solution was poured into cold water. The precipitated solid was collected by filtration, washed with water, and dried, yielding 1 g (54%) of **6**. The product was crystallized from ethanol for analytical purposes: mp 175−177 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.73 (1H, bs), 8.12−8.07 (2H, m), 7.81 (1H, bs), 7.69 (1H, tt, J = 7.3, 1.3 Hz), 7.63 (1H, dd, J = 7.9, 1.5 Hz), 7.57 (2H, t, J = 7.5 Hz), 7.32−7.25 (1H, m), 7.15 (1H, bs), 6.76 (1H, d, J = 8.4 Hz), 6.58 (1H, t, J = 7.5 Hz), 4.80 (2H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 195.5, 171.3, 148.7, 135.0, 133.6, 132.4, 128.9, 128.8, 127.8, 114.5, 114.3, 112.0, 49.7. IR (KBr, cm^{-1}): 3367, 3236, 1731, 1643, 1632, 1618, 1513. CI(methane)-MS; full MS, *m*/*z* (relative intensity) 255 (40) $[M + H]^+$, 283 $[M + C_2H_5]^+$, 295 $[M + C_3H_5]^+$, 238 (100) $[M + H - NH_3]^+$, 194 $[C_6H_5NHCHCH\ C_6H_5]^+$; MS^2-(255,w5,EV1), *m*/*z* 238, 220, 212, 194, 149, 132, 120. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.61; H, 5.55; N, 10.98.

3-Amino-2-phenyl-4(1*H*)-quinolinone (7a). Method A: Anthranilamide **2a** (2 g, 7.87 mmol) was mixed with polyphosphoric acid (20 g), and the reaction mixture was heated to 150 °C. After heating for 1.5 h at this temperature, the starting material was no longer observed in TLC (ethyl acetate). The reaction mixture was poured onto sodium carbonate (20 g), and after foaming had stopped, water (300 mL) was added. After 30 min of stirring, a solid product was filtered off and washed with water. The yield of the product **7a** was 1.8 g (97%): mp 250−253 °C. Using HPLC, we found its purity to be 98%. Crystallization was carried out for analytical purposes: mp 256−259 °C (acetone) (lit:[10] mp 243−245 °C, aqueous ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.44 (1H, s), 8.12 (1H, d, J = 8.2 Hz), 7.75−7.70 (2H, m), 7.65−7.47 (5H, m), 7.24−7.17 (1H, m), 4.22 (2H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.7, 137.6, 133.7, 129.8, 129.7, 129.1, 128.9, 128.8, 127.9, 124.6, 121.3, 120.6, 118.1. IR (KBr, cm^{-1}): 3346, 1633, 1570, 1493. CI(methane)-MS; full MS, *m*/*z* (relative intensity) 237 (100) $[M + H]^+$, 265 $[M + C_2H_5]^+$, 277 $[M + C_3H_5]^+$, 220 $[M + H - NH_3]^+$; MS^2(237,w5,EV1.5), *m*/*z* 235, 220, 208, 206, 190, 180, 165, 152, 132, 104. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.00; H, 5.14; N, 11.80.

Method B: Diazepine **4a** (250 mg, 1.058 mmol) was stirred with polyphosphoric acid (5 g) at 150 °C. After an hour at this temperature, the starting material could no longer be observed in TLC (ethyl acetate). The reaction mixture was poured over solid sodium carbonate (5 g). After foaming had stopped, water (60 mL) was added. After 30 min of stirring, the solid product was filtered off and washed with water. The yield of the product **7a** was 225 mg (90%): mp 256−259 °C.

Method C: Oxazole derivative **3a** (336 mg, 1.42 mmol) was stirred with polyphosphoric acid (3.4 g), and the reaction mixture was heated to 170 °C for 2 h. The reaction mixture was poured onto sodium carbonate (5 g), and after foaming had stopped, water (30 mL) was added. After 30 min of stirring, the solid product was filtered off and washed with water. The yield of the product **7a** was 306 mg (91%). mp 254−258 °C (acetone).

Method D: Anthranilamide **6** (250 mg, 0.983 mmol) was stirred with polyphosphoric acid (5 g), and the reaction mixture was heated to 140 °C for 2 h. After the starting material could no longer be

observed in TLC (ethyl acetate), the reaction mixture was poured over solid sodium carbonate (10 g), and after foaming had stopped, water (150 mL) was added. The solution was subsequently extracted using ethyl acetate. The organic solution was evaporated to dryness and the residuum was separated by column chromatography on silica gel with ethyl acetate as eluent. Three main products were separated. Product **7a** was isolated in yield of 100 mg (43%): mp 253−255 °C (acetone).

Method E: Anthranilamide **2a** (500 mg, 1.97 mmol) was mixed with 85% phosphoric acid (10 mL), and the reaction mixture was heated to 140 °C (reflux). After 2 h of heating, the starting material was no longer observed in TLC (ethyl acetate). The reaction mixture was poured onto sodium carbonate (5 g), and after foaming had stopped, water (75 mL) was added. After 30 min of stirring, a solid product was filtered off and washed with water. The yield of the product **7a** was 440 mg (95%): mp 251−253 °C.

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Supporting Information Available: HPLC procedure for compounds **2a**, **4a**, and **7a** and results of analysis of the reaction mixture. Information about synthesis and analysis of compounds **2b**−**k** and **7b**−**k**. X-ray crystallographic data for compound **7a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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