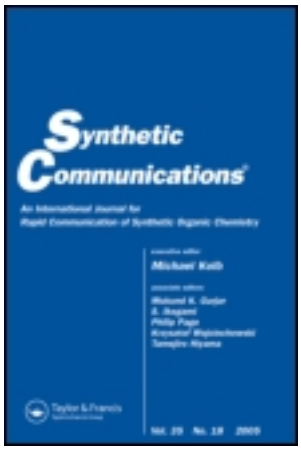

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AN IMPROVED METHOD FOR THE SYNTHESIS OF 3-AMINO-1H-QUINOLIN-2-ONE

Cecilia Juárez-Gordiano [a] , Alicia Hernández-Campos, [a] & Rafael Castillo [b]

[a] Departamento de Farmacia, Facultad de Química UNAM, CU, México, DF 04510, México

[b] Departamento de Farmacia, Facultad de Química UNAM, CU, México, DF 04510, México

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AN IMPROVED METHOD FOR THE SYNTHESIS OF 3-AMINO-1*H*-QUINOLIN-2-ONE

Cecilia Juárez-Gordiano, Alicia Hernández-Campos, and Rafael Castillo*

Departamento de Farmacia, Facultad de Química
UNAM, CU. México DF 04510, México

ABSTRACT

An efficient method for the synthesis of 3-amino-1*H*-quinolin-2-one is described. Condensation of *o*-nitrobenzaldehyde with hippuric acid gave 4-(2-nitrobenzylidene)-2-phenyloxazol-5-one. This compound was reduced to give 4-(2-aminobenzylidene)-2-phenyloxazol-5-one, which upon isomerization with light, cyclization and hydrolysis afforded the desired product.

Key Words: 3-Amino-1*H*-quinolines; Synthesis; Photochemical isomerization

The considerable biological importance of quinolone derivatives, such as antibacterial activity[1] and, more recently, antiviral activity[2] has stimulated work on these heterocycles. This is the case of 3-amino-1*H*-quinolin-2-one (**6**). As part of our studies to prepare new agents with potential antiviral activity we were in need of **6**; however, there are no general methods available for its preparation in good yields.

*Corresponding author. Fax: +(525)6225329; E-mail: rafaelc@servidor.unam.mx

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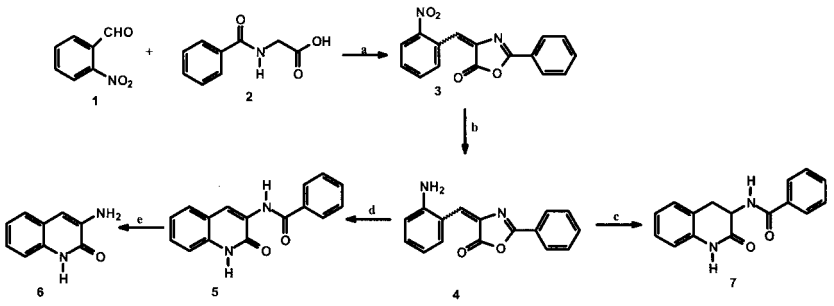
One approach reported is based on the condensation of 2-aminobenzaldehyde with α-nitromethylenecarbonyl compounds with a subsequent cyclization and reduction of the nitro group to give **6**. However, this method gives very poor yields.[3] In another approach, the condensation of 2-nitrobenzaldehyde with aceturic acid gave a mixture of *cis* and *trans* 2-methyl-4-(2-nitrobenzylidene)oxazol-2-one, which upon separation, reduction of the *cis* isomer, cyclization, and hydrolysis gave **6** in low yield.[4] The synthesis of **6** has also been achieved via a Curtius rearrangement; nevertheless, this method involves a multistep process giving low yields of **6**.[5] And finally, **6** was obtained by the reduction of methyl anthranilate, followed by oxidation of the corresponding alcohol. Condensation of this with ethyl nitroacetate gave 3-nitroquinolone, which upon hydrogenation afforded the product.[6]

In this paper we describe a short and efficient synthesis of 3-amino-1*H*-quinolin-2-one according to reaction Sch. 1.

The condensation of *o*-nitrobenzaldehyde (**1**) and hippuric acid (**2**) in acetic anhydride containing pyridine as a base at 75°C gave a 91% yield of 4-(2-nitrobenzylidene)-2-phenyloxazol-5-one (**3**). Catalytic reduction of **3** with H_2, Pd/C 5% for 15 min afforded a 93% yield of a red crystalline material identified as 4-(2-aminobenzylidene)-2-phenyloxazol-5-one (**4**). Its ^{1}H NMR spectrum showed a broad signal at 6.23 ppm because of the NH_2 group. When the hydrogenation time increased to 30 min, 3-benzamido-3,4-dihydro-1*H*-quinolin-2-one (**7**) was obtained. These results support the idea that the geometry of **4** and **3** is *trans* in such a way that the reacting carbonyl and amino groups are on opposite sides of the double bond; for this reason **5** was not obtained directly under these conditions. Later on, **4** was isomerized and cyclized upon irradiation with a 250-Watt G.E. sunlamp in acetone as a solvent. In this reaction, the product was



Scheme 1. (a) Ac_2O, pyridine, 75°C; (b) H_2, Pd/C 5%, ethanol, 15 min; (c) H_2, Pd/C 5%, ethanol, 30 min; (d) Light, acetone; (e) NaOH–H_2O/EtOH, 80°C.

3-benzamido-1*H*-quinolin-2-one (**5**), which precipitated as soon as it was formed in 80% yield. Finally, **5** was hydrolyzed in $EtOH/H_2O$ with NaOH at 80°C for 48 h to afford **6** in 92% yield. All compounds obtained had IR, ^1H NMR, MS spectra and elemental analysis, which are consistent with the expected structures.

In conclusion, in this communication an efficient method is described for the synthesis of **6** in only four steps, each of which with good yields. The important feature of this work is the high selectivity in the condensation reaction where only one isomer is formed, and not a mixture of isomeric oxazolones, as described in the case of aceturic acid.[4] The catalytic hydrogenation of **3** was also selective, since only the nitro group was reduced in preference to the exocyclic double bond. Each reaction step in the synthesis is simple to carry out, affording good product yields, which are higher than those previously reported in the literature.

EXPERIMENTAL

Melting points were determined with a Buchi 530 model apparatus and are uncorrected. IR spectra were taken on a Perkin Elmer spectrometer. ^1H NMR spectra were recorded on a Varian VXR-300 spectrometer, using TMS as internal standard. Mass spectra (MS) were performed by EI, 70 eV, using a Hewlett Packard apparatus, model 5988.

4-(2-Nitrobenzylidene)-2-phenyloxazol-5-one (3): A mixture of **1** (25.00 g, 0.1654 mol), **2** (36.00 g, 0.2009 mol), acetic anhydride (31.61 mL) and pyridine (13.54 mL) was stirred for 15 min at 75°C and a dark brown solid was formed. The mixture was filtered, and the residue was washed with ethanol. The crude product was purified by recrystallization from toluene to give 44.33 g (0.1506 mol, 91.05%) of yellow crystals, m.p. 162–164°C. ^1H NMR ($CDCl_3$): δ 8.68 (dd, $J = 7.80$ and 1.20 Hz, 1H, H-6′), 8.18–8.10 (m, 2H, H-4′, 5′), 8.06 (dd, $J = 8.40$ and 1.20 Hz, 1H, H-3′), 7.81 (td, $J = 7.65$ and 1.50 Hz, 1H, H-4″), 7.61 (s, 1H, H-benzylic), 7.71–7.56 (4H, m, H-2″, 3″, 5″, 6″); IR (KBr): 1850 (C=O), 1798 (C=N) 1514 and 1334 (NO_2) cm^{-1}; MS: m/z 294 (M^+, 17%), 105 (100%); Anal. Calcd: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.27; H, 3.18; N, 9.49.

4-(2-Aminobenzylidene)-2-phenyloxazol-5-one (4): A mixture of **3** (15.00 g, 0.0510 mol), ethyl acetate (200 mL) and 5% Pd/C (1.50 g) was hydrogenated (60 psi) in a Parr hydrogenation apparatus for 15 min at room temperature. The resulting solution was filtered and the solvent, evaporated. The residue was recrystallized from toluene to give 12.60 g (0.0477 mol, 93.53%) of red crystals, m.p. 172–173°C. ^1H NMR ($CDCl_3$):

δ 8.18 (dd, $J = 8.10$ and 1.50 Hz, 1H, H-6′), 8.08 (dd, $J = 7.70$ and 1.50 Hz, 2H, H-2″, 6″), 7.75–7.51 (m, 3H, H-3″, 4″, 5″), 7.47 (s, 1H, H-benzylic), 7.16 (td, $J = 7.72$ and 1.50 Hz, 1H, H-5′), 6.75 (dd, $J = 7.90$ and 1.20 Hz, 1H, H-3′), 6.65 (td, $J = 7.80$ and 1.20 Hz, 1H, H-4′), 6.23 (s, 2H, NH_2); IR (KBr): 3402 and 3334 (NH_2), 1770 (C=O), 1646 (C=N) cm^{-1}; MS: m/z 264 (M^+, 100%), 105 (5%); Anal. Calcd: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.76; H, 4.11; N, 10.18.

3-Benzamido-1*H*-quinolin-2-one (5): Compound **4** (10.00 g, 0.0378 mol) was suspended in acetone (200 mL) and the mixture was stirred and irradiated with a 250-Watt G.E. sunlamp for 3 days. During this time red crystals were formed. The mixture was filtered and the residue was washed with acetone and recrystallized from ethanol to give 8.00 g (0.0303 mol, 80.16%) of **5**, m.p. 271–273°C. ^{1}H NMR: ($CDCl_3$–DMSO-d_6): δ 12.36 (s, 1H, NH, benzamide), 9.36 (s, 1H, NH quinolone), 8.72 (s, 1H, H-4), 7.91 (dd, $J = 7.50$ and 1.80 Hz, 2H, H-2′, 6′), 7.64–7.48 (m, 4H, H-5, H-3′, 4′, 5′), 7.40–7.31 (m, 2H, H-6, 7), 7.16–7.27 (m, 1H, H-8); IR (KBr): 3370 (NH), 1682 (C=O), 1644 (C=O) cm^{-1}; MS: m/z 264 (M^+, 65%), 78 (100%); Anal. Calcd: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.28; H, 4.44; N, 10.49.

3-Amino-1*H*-quinolin-2-one (6): To a solution of NaOH (11.00 g, 0.275 mol) in water (59 mL) and ethanol (35 mL) was slowly added **5** (6.60 g, 0.0250 mol) and the resulting mixture was stirred at 80°C for 48 h. After cooling, water (100 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent under vacuum gave 3.70 g, (0.0231 mol, 92.40%) of a light yellow solid, m.p. 208–209°C, [lit.[4,5] 210–211°C]. ^{1}H NMR ($CDCl_3$–DMSO-d_6): δ 11.79 (s, 1H, NH), 7.32 (d, $J = 7.50$, 1H, H-5), 7.19 (d, $J = 7.80$, 1H, H-8), 7.11 (t, $J = 7.50$ and 1.50 Hz, 1H, H-7), 7.02 (t, $J = 7.20$ and 1.50 Hz, 1H, H-6), 6.72 (s, 1H, H-4), 5.44 (s, 2H, NH_2); IR (KBr): 3440 and 3334 (NH_2), 1668 (C=O) cm^{-1}; MS: m/z 160 (M^+, 100%), 133 (64%), 105 (41%); Anal. Calcd: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.11; H, 5.00; N, 17.22.

3-Benzamido-3,4-dihydro-1*H*-quinolin-2-one (7): A mixture of **3** (16.00 g, 0.0544 mol), ethyl acetate (200 mL) and 5% Pd/C (1.50 g) was shaken under hydrogen (60 psi) in a Parr hydrogenation apparatus for 30 min at room temperature. The catalyst was removed by filtration and the product crystallized spontaneously in the filtrate to give 11.50 g, (0.0432 mol, 79.41%) of **7**, m.p. 166–167°C. ^{1}H NMR ($CDCl_3$): δ 10.2 (s, 1H, NH quinolone), 8.07 (d, $J = 6.60$ Hz, 1H, NH benzamide), 7.91 (dd, $J = 6.60$ and 1.50 Hz, 2H, H-5, 8), 7.57–7.41 (m, 3H, H-3′, 4′, 5′), 7.22–7.12 (m, 2H, 2′, 6′), 7.01–6.91 (m, 2H, H-6, 7), 4.83–4.71 (m, 1H, H-3), 3.39–3.28 (m, 2H, CH_2); IR (KBr): 3300 (NH), 1692 (C=O) cm^{-1}; MS:

m/*z* 266 (M^+, 1%), 145 (100%); Anal. Calcd: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.88; H, 5.14; N, 10.40.

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