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A new synthetic approach for the preparation of substituted 2(1*H*)-quinolinones **5** from readily available anilines has been developed. The four step procedure resulted in the synthesis of a variety of substituted 2(1*H*)-quinolinones in good yields and under mild reaction conditions.

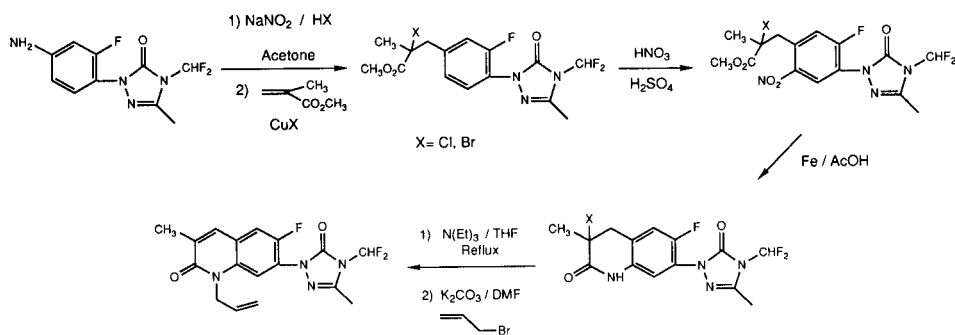
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Quinolines in general and 2(1*H*)-quinolinones in particular have been the subject of intense study [1]. We have previously described a novel synthesis of a variety of biologically active 1,3,6,7-tetrasubstituted 2(1*H*)-quinolinone compounds (Scheme 1) [2]. These molecules are potent herbicides which act by inhibiting protoporphyrinogen oxidase in plants [3].

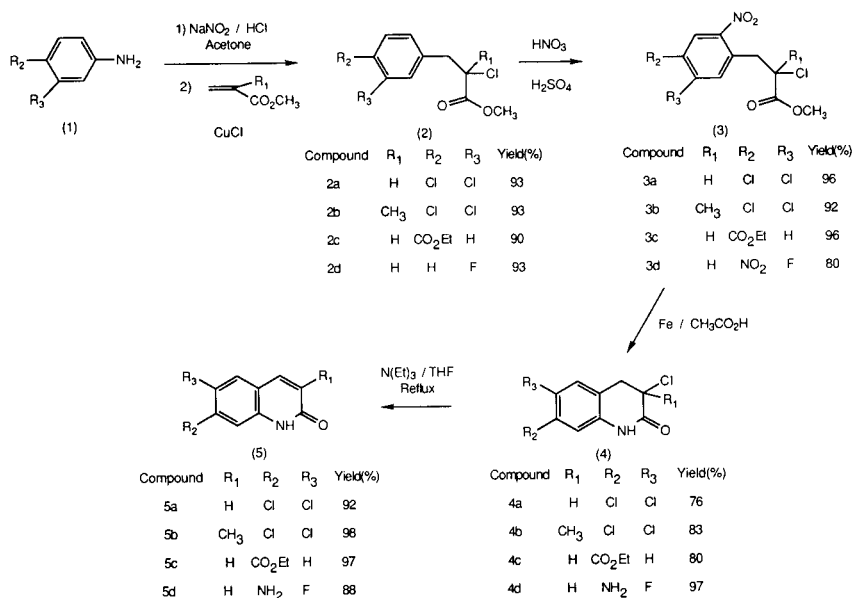
In the present work we would like to extend this approach to the synthesis of several other mono, di, and tri-substituted 2(1*H*)-quinolinones of general structure **5**. The

new procedure relies upon a four step reaction sequence involving the use of the Meerwein reaction [4] to prepare the methyl α -chloro- β -arypropionate intermediates **2** from readily available anilines **1** (Scheme 2). The anilines were diazotized with nitrous acid in acetone to give the intermediate benzenediazonium chlorides which are reacted, without isolation, with excess methyl acrylate or methyl methacrylate in the presence of catalytic amounts of cuprous chloride to give the desired intermediates in excellent yields. A relatively large excess of methyl acrylate

Scheme 1



Scheme 2



or methyl methacrylate (10-fold) relative to the substituted arylamine was used in these reactions. Lower yields of the α -chloro- β -arylpropionates **2** were obtained when only a five fold excess of the methyl acrylate or methacrylate were used. Methyl α -chloro- β -arylpropionates **2** were also obtained from the addition of the appropriate aniline to a solution of acetonitrile, alkyl nitrite, anhydrous copper(II) chloride, and a large excess of methyl acrylate [5]. By this procedure compound **2a** was obtained in 64% yield.

The α -chloro- β -arylpropionates **2** were nitrated in concentrated sulfuric acid at 10°, to give the corresponding α -chloro- β -(2-nitrophenyl)propionate derivatives **3**. Dinitration of methyl α -chloro- β -(3-fluorophenyl)propionate (**2d**) was accomplished by employing a large excess, 5 equivalents, of nitric acid and allowing the temperature to reach 40° while addition takes place.

The α -chloro- β -(2-nitrophenyl)propionate derivatives **3** were reductively cyclidized with iron in acetic acid in good yields. Attempts to obtain compound **4** by catalytic hydrogenation with PtO₂ or Pd(C) in ethanol resulted in extensive hydrogenolysis side reactions [6]. Conversion of compounds **4a-d** to the corresponding substituted 2(1*H*)-quinolinones was achieved by the use of triethylamine in tetrahydrofuran in high yields. The structures of intermediates **2** and **3**, the various reductive cyclization products **4**, and the final products **5** were all correlated with their proton nmr spectra.

In conclusion, the present methodology demonstrates an efficient, regioselective, and mild synthesis of a variety of polysubstituted 2(1*H*)-quinolinones from readily available anilines.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Nicolet QE 300 NMR spectrometer and reference to TMS and deuteriochloroform or deuterated dimethyl sulfoxide as the solvent. Infrared spectra were determined on a Nicolet 52 DX FT-IR spectrophotometer using the potassium bromide technique. Elemental analysis were performed at FMC Corporation, Analytical Services Department.

Synthesis of Methyl α -Chloro- β -arylpropionates.

Compound **2a**.

To a solution of 3,4-dichloroaniline (8.10 g, 0.050 mole), acetone (120 ml) and concentrated hydrochloric acid (20 ml) was added a solution of sodium nitrite (3.50 g, 0.050 mole) in water (10 ml) while keeping the temperature below 10°. The reaction was stirred at 10° for one hour when methyl acrylate (43.04 g, 0.50 mole) was added and the reaction was cooled down to 0°. Cuprous chloride (300 mg) was added slowly, the temperature rose to 10°, and evolution of nitrogen gas was observed. After addition of cuprous chloride was completed the reaction was allowed to stir at room temperature for one hour, diluted with water (200 ml) and extracted with ether. After removal of the ether and excess methyl acrylate under reduced pressure, the residue was

chromatographed on a silica gel column with methylene chloride as eluent to give 12.70 (93%) of an oil; ir (neat): 1750 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): 3.09-3.36 (m, 2H, CH₂), 3.75 (s, 3H, OCH₃), 4.44 (t, 1H), 7.06-7.38 (m, 3H, aryl).

Anal. Calcd. for C₁₀H₉Cl₂O₂: C, 44.89; H, 3.39; Cl, 39.75. Found: C, 44.87; H, 3.46; Cl, 39.43.

By the above procedure the following compounds were prepared:

Compound **2b**.

This compound was obtained from 3,4-dichloroaniline and methyl methacrylate in 93% yield (oil); ir (neat): 1750 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): 1.72 (s, 2H, CH₃), 3.24 (s, 2H, CH₂), 3.76 (s, 3H, CH₂), 7.04-7.37 (m, 3H, aryl).

Anal. Calcd. for C₁₁H₁₁Cl₂O₂: C, 46.92; H, 3.95; Cl, 37.77. Found: C, 47.18; H, 3.97; Cl, 38.04.

Compound **2c**.

This compound was obtained from ethyl 4-aminobenzoate and methyl acrylate in 90% yield (oil); ir (neat): 1750 (CO) cm⁻¹, 1720 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): 1.38 (t, 3H, CH₃), 3.20-3.48 (m, 2H, CH₂), 3.70 (s, 3H, OCH₃), 4.38 (q, 2H, OCH₂), 4.48 (t, 1H), 7.30 (d, 2H, J_{HH} = 8.17 Hz, aryl), 7.95 (d, 2H, J_{HH} = 8.17 Hz, aryl).

Anal. Calcd. for C₁₃H₁₅ClO₄: C, 57.68; H, 5.58; Cl, 13.09. Found: C, 57.54; H, 5.78; Cl, 13.41.

Compound **2d** [7].

This compound was obtained from 3-fluoroaniline and methyl acrylate in 93% yield (oil); ir (neat): 1750 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): 3.12-3.39 (m, 2H, CH₂), 3.74 (s, 3H, OCH₃), 4.44 (t, 1H), 6.91-7.27 (m, 4H, aryl).

Anal. Calcd. for C₁₀H₁₀ClFO₂: C, 55.44; H, 4.66; Cl, 16.37; F, 8.77. Found: C, 55.43; H, 4.65; Cl, 16.11; F, 8.65.

Nitration of Methyl α -Chloro- β -arylpropionates to Give Compounds **3a-d**.

Compound **3a**.

Methyl α -chloro- β -(3,4-dichlorophenyl)propionate (**2a**) (5.34 g, 0.020 mole) in concentrated sulfuric acid (45 ml) was cooled to 10°. Nitric acid (1.54 ml, 70% concentration, 0.024 mole) was added dropwise while maintaining the temperature of the reaction at 10°. After the addition was completed the reaction mixture was allowed to stir at room temperature for one hour, poured into ice and extracted with ether. Removal of the ether under reduced pressure gave a residue which was chromatographed on a silica gel column with dichloromethane as eluent to give 6.0 g (96%) of the desired product mp 43-44°; ir (potassium bromide): 1750 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): 3.32-3.76 (m, 2H, CH₂), 3.80 (s, 3H, OCH₃), 4.66 (1H), 7.57 (s, 1H, aryl), 8.19 (s, 1H, aryl).

Anal. Calcd. for C₁₀H₈Cl₂NO₄: C, 38.43; H, 2.59; Cl, 34.03; N, 4.48. Found: C, 38.63; H, 2.46; Cl, 33.97; N, 4.80.

By the above procedure the following compounds were prepared:

Compound **3b**.

This compound was obtained from the nitration of **2b** in 92% yield as an oil; ir (neat): 1740 (CO) cm⁻¹; ¹H nmr (deuteriochloroform): 1.74 (s, 3H, CH₃), 3.68 (d, 1H, J_{HH} = 15 Hz, CH₂), 3.84 (d, 1H, J_{HH} = 15 Hz, CH₂), 3.71 (s, 3H, OCH₃), 7.61 (s, 1H, aryl), 8.05 (s, 1H, aryl).

Anal. Calcd. for $C_{11}H_{10}Cl_3NO_4$: C, 40.46; H, 3.09; Cl, 32.57; N, 4.29. Found: C, 40.64; H, 2.93; Cl, 32.38; N, 4.50.

Compound 3c.

This compound was obtained from the nitration of **2c** in 96% yield as an oil; ir (neat): 1750 (CO), 1725 (CO) cm^{-1} ; 1H nmr (deuteriochloroform): 1.40 (t, 3H, CH_3), 3.40-3.80 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 4.41 (q, 2H, OCH_2), 4.69 (t, 1H), 7.54 (d, 1H, $J_{HH} = 8.0$ Hz, aryl), 8.21 (d, 1H, $J_{HH} = 8.0$ Hz, aryl), 8.64 (s, 1H, aryl).

Anal. Calcd. for $C_{13}H_{14}ClNO_6$: C, 49.46; H, 4.47; Cl, 11.23; N, 4.43. Found: C, 49.34; H, 4.35; Cl, 11.40; N, 4.32.

Compound 3d.

A solution of nitric acid (2.93 ml, 70% concentration, 0.046 mole) and concentrated sulfuric acid (3 ml) were added dropwise to a mixture of methyl α -chloro- β -(3-fluorophenyl)propionate (**2d**) (2.0 g, 0.0092 mole) in concentrated sulfuric acid while maintaining the temperature of the reaction below 40°. When addition was completed the reaction was allowed to stir at room temperature for an additional two hours, after which it was poured into ice and extracted with ethyl acetate. Removal of the ethyl acetate under reduced pressure gave a residue which was chromatographed on silica gel column with methylene chloride as eluent to give 80% of **3d** as a thick oil; ir (potassium bromide): 1750 (CO) cm^{-1} ; 1H nmr (deuteriochloroform): 3.45-3.90 (m, 2H, CH_2), 3.84 (s, 3H, CH_3), 4.70 (t, 1H), 7.49 (d, 1H, $J_{HF} = 10.65$ Hz, aryl), 8.87 (d, 1H, $J_{HF} = 6.77$ Hz, aryl).

Anal. Calcd. for $C_{13}H_9ClFN_2O_6$: C, 39.17; H, 2.63; Cl, 11.56; F, 6.19; N, 9.13. Found: C, 39.11; H, 2.66; Cl, 11.30; F, 6.11; N, 9.00.

Synthesis of Substituted 3,4-Dihydro-2(1*H*)-quinolinone.

Compound 4a.

Methyl α -chloro- β -(3,4-dichloro-2-nitrophenyl)propionate (**3a**) (4.55 g, 0.014 mole), water (4 ml) and glacial acetic acid (60 ml) were heated to 50°. Iron powder (4.5 g, 0.080 mole) was slowly added while keeping the temperature at 50°. When addition was completed the reaction was allowed to stir for an additional two hours at 50°. The solution was allowed to cool down to room temperature, diluted with ethyl acetate and filtered through a Celite pad. The acetic acid/ethyl acetate solution was diluted with water (300 ml) and the organic layer washed several times with water. Ethyl acetate was removed under reduced pressure and the solid recrystallized from acetone/heptane to give 2.76 g (76%) of **4a**, mp 203-204°; ir (potassium bromide): 1690 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 3.19-3.56 (m, 2H, CH_2), 4.79 (t, 1H), 7.10 (s, 1H, aryl), 7.60 (s, 1H, aryl), 10.76 (s, 1H, NH).

Anal. Calcd. for $C_9H_8Cl_2NO$: C, 43.15; H, 2.42; Cl, 42.46; N, 5.59. Found: C, 43.11; H, 2.41; Cl, 42.43; N, 5.59.

By the above procedure the following compounds were prepared:

Compound 4b.

Reduction of **3b** with iron powder gave 83% of a solid mp 230-231° (recrystallized from methanol); ir (potassium bromide): 1685 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 1.78 (s, 3H, CH_3), 3.34 (d, 1H, $J_{HH} = 15$ Hz, CH_2), 3.48 (d, 1H, $J_{HH} = 15$ Hz, CH_2), 7.11 (s, 1H, aryl), 7.57 (s, 1H, aryl), 10.75 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_8Cl_2NO$: C, 45.40; H, 3.05; Cl, 40.20; N, 5.30. Found: C, 45.70; H, 2.85; Cl, 40.09; N, 5.51.

Compound 4c.

Reduction of **3c** with iron powder gave 80% of a solid mp

173-174° (recrystallized from ethyl acetate/heptane); ir (potassium bromide): 1710 (CO), 1685 (CO) cm^{-1} ; 1H nmr (deuteriochloroform): 1.40 (t, 3H, CH_3), 3.27-3.55 (m, 2H, CH_2), 4.40 (q, 2H, OCH_2), 4.63 (t, 1H), 7.30 (d, 1H, $J_{HH} = 4$ Hz, aryl), 7.63 (s, 1H, aryl), 7.76 (d, 1H, $J_{HH} = 4.0$ Hz, aryl), 8.89 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{12}ClNO_5$: C, 56.82; H, 4.76; Cl, 14.01; N, 5.51. Found: C, 56.50; H, 4.69; Cl, 14.31; N, 5.42.

Compound 4d.

Reduction of methyl α -chloro- β -(2,4-dinitro-5-fluorophenyl)propionate (**3d**) (2.64 g, 0.0080 mole) with iron powder (3.96 g, 0.070 mole) by the same procedure outlined for **4a** gave 1.80 g (97%) of a solid mp 194-195° (recrystallized from acetone/water); ir (potassium bromide): 3440, 3380 (NH₂), 1680 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 2.92-3.30 (m, 2H, CH_2), 4.68 (t, 1H), 5.14 (bs, 2H, NH₂), 6.36 (d, 1H, $J_{HF} = 8.0$ Hz, aryl), 6.92 (d, 1H, $J_{HF} = 11.0$ Hz, aryl), 10.32 (s, 1H, NH).

Anal. Calcd. for $C_9H_8ClFN_2O$: C, 50.36; H, 3.76; Cl, 16.52; F, 8.85; N, 13.06. Found: C, 50.44; H, 3.65; Cl, 16.76; F, 8.65; N, 12.95.

Synthesis of Substituted 2(1*H*)-Quinolinones.

Compound 5a.

3,6,7-Trichloro-3,4-dihydro-2(1*H*)-quinolinone (**4a**) (1.0 g, 0.0039 mole), tetrahydrofuran (50 ml) and triethylamine (2.50 ml, 0.018 mole) were refluxed for 18 hours. Removal of the solvent under reduced pressure gave a white solid which was washed well with water, yield = 0.65 g (92%) of **5a** mp 289-290° (recrystallized from methanol); ir (potassium bromide): 1670 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 6.58 (d, 1H, $J_{HH} = 9.50$ Hz, olefinic H), 7.46 (s, 1H, aryl), 7.86 (d, 1H, $J_{HH} = 9.50$ Hz, olefinic H), 8.02 (s, 1, aryl).

Anal. Calcd. for $C_9H_5Cl_2NO$: C, 50.50; H, 2.36; Cl, 33.12; N, 6.55. Found: C, 50.69; H, 2.22; Cl, 33.40; N, 6.45.

By the above procedure the following compounds were prepared:

Compound 5b.

Compound **5b** was obtained in 98% yield, mp 307-308° (recrystallized from ethyl acetate/acetone); ir (potassium bromide): 1670 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 2.10 (s, 3H, CH_3), 7.44 (s, 1H, aryl), 7.68 (s, 1H, C₄H), 7.79 (s, 1H, aryl), 11.88 (bs, 1H, NH).

Anal. Calcd. for $C_{10}H_7Cl_2NO$: C, 52.66; H, 3.09; Cl, 31.08; N, 6.13. Found: C, 52.42; H, 2.85; Cl, 30.69; N, 6.08.

Compound 5c.

Compound **5c** was obtained in 97% yield as a solid, mp 235-236° (crystallized from methanol); ir (potassium bromide): 1715 (CO), 1660 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 1.35 (t, 3H, CH_3), 4.35 (q, 2H, OCH_2), 6.64 (d, 1H, $J_{HH} = 9.5$ Hz, C₃H), 7.68-7.99 (m, 4H, aryl and C₄H), 11.91 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.10; N, 6.44. Found: C, 66.19; H, 5.33; N, 6.41.

Compound 5d.

Compound **5d** was obtained in 88% yield as a solid, mp 284-285° dec (recrystallized from ethyl acetate/acetone); ir (potassium bromide): 3330, 3200 (NH₂), 1659 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): 5.91 (bs, 2H, NH₂), 6.12 (d, 1H, $J_{HH} = 9.40$ Hz, aryl), 6.58 (d, 1H, $J_{HF} = 8.0$ Hz), 7.27 (d, 1H, $J_{HF} = 11.60$ Hz, aryl), 7.61 (d, 1H, $J_{HH} = 9.40$ Hz, C₃H), 11.41 (bs, 1H, NH).

Anal. Calcd. for $C_9H_7FN_2O$: C, 60.67; H, 3.97; F, 10.66; N, 15.73. Found: C, 60.79; H, 3.67; F, 10.46; N, 15.53.

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