

A Novel Short-Step Synthesis of Functionalized 4-Hydroxy-2-quinolones Using a 1-Hydroxybenzotriazole Methodology

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A novel method for the synthesis of 3-substituted 4-hydroxy-1-methyl- and 1-phenyl-2-quinolones is presented. The compounds are produced in a one-step reaction in very good yields (51–76%). The major advantage of the methodology is the short time for the synthesis in contrast to previous methodologies requiring several steps and harsh conditions for the synthesis of quinolone derivatives.

4-Hydroxy-2-quinolones (Fig. 1) constitute an important class of heterocyclic compounds with widespread biological action. This class of compounds is comprised of many alkaloids isolated from a variety of plants such as *Haplophyllum tuberculatum*,[1] *Galipea Officinalis*,[2] and *Glycosmis citrifolia*.[3] These alkaloids have shown remarkable biological and pharmacological properties, such as antimicrobial, anticoccidial, and antitumor activities.[4–8] Particularly, compounds bearing a methyl group attached to *N*-1 have shown anti-inflammatory and antithyroid activity.[9,10] Recently, a series of quinoline-3-carbothioamides have shown antinephritic and immunomodulating activity,[11] whereas a novel 1-methylquinolone derivative, designed as an antioxidant to scavenge reactive oxygen species, may be of therapeutic use for bronchial asthma.[12] Antagonistic activity against the glycine site of the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor has also been reported for 4-hydroxy-2-quinolones.[13,14] Finally, 1-methylquinoline derivatives have been used for treatment of mammals suffering from autoimmune and pathological inflammation[15] diseases and a prostaglandin E mediated condition.[16]

Many research groups have been involved in the synthesis of functionalized quinolines. The most common route to these compounds is the use of anthranilic acid and active methylene compounds as acylating agents.[17,18] Coppola's group has published some very good results on this subject using isatoic anhydrides as starting materials.[19,20] Our research group has also been involved in the synthesis of 3-substituted quinoline-2,4-(1*H*,3*H*)-dione[21] and quinoline alkaloid analogues.[22] We have recently presented a very flexible one-step method for the synthesis of tetramic acids,[23] tetronic acids,[24] and functionalized butenoates.[25] We attempted to apply this methodology to the synthesis of "quinolones" by using as starting materials *N*-methyl- or *N*-phenylanthranilic acid activated with 1-hydroxybenzotriazole for elaboration of different types of quinolinone skeletons. In this paper, we report the "one-pot" synthesis of 3-substituted 4-hydroxy-1-methyl- and 1-phenyl-2-quinolones starting from the activated 1-hydroxybenzotriazole ester of the appropriate *N*-substituted anthranilic acid and a suitable active methylene compound as building blocks. This approach allows for a wide variation of the substitution pattern of the "quinolone" ring at the 1 and 3 position (Scheme 1).

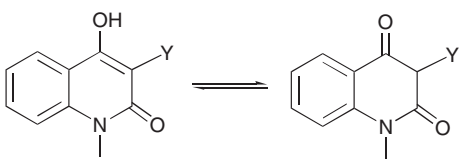

Fig. 1. 3-Substituted 4-hydroxy-2-quinolones.

The proposed strategy consists of a *C*-acylation reaction between an active methylene compound **3a**–**3d** and the 1-hydroxybenzotriazole ester of the *N*-substituted anthranilic acid **1a**–**b**. The requisite 1-hydroxybenzotriazole ester of the *N*-alkylanthranilic acid was synthesized by condensation of equimolar amounts of **1a** or **1b** with 1-hydroxybenzotriazole and dicyclohexylcarbodiimide (DCC) in anhydrous THF at 0 °C. After a reaction time of 24 h, the reaction mixture was filtered and the filtrate containing the non-isolated active ester was used as the acylating agent in the next step. In a typical *C*-acylation reaction the active methylene compound **3a**–**3d** (1 molar amount) was treated with sodium hydride (2 molar amounts) in anhydrous THF at r.t. and then the active ester solution was added. After stirring for 2.5 h, the solvent was removed under reduced pressure, the residue was diluted with water, washed with diethyl ether and the aqueous layer was acidified with 10% HCl to give the 3-substituted 4-hydroxy-1-methyl- and 1-phenyl-2-quinolones **4**–**8** or the *C*-acylation compounds **9** and **10**. Cyclization of the *C*-acylation compounds **9** and **10** to the corresponding 3-cyano-4-hydroxy-1-phenyl-2-quinolone **11** was accomplished by treatment with a methanolic 10% HCl solution at r.t. for 48 h.

Remarkably, the type of product obtained from the *C*-acylation–cyclization reaction depends on the *N*-substituent of anthranilic acid and the active methylene compound used. Thus, utilization of dimethyl and diethyl malonate resulted in the formation of the 3-substituted 4-hydroxy-1-methyl- and 1-phenyl-

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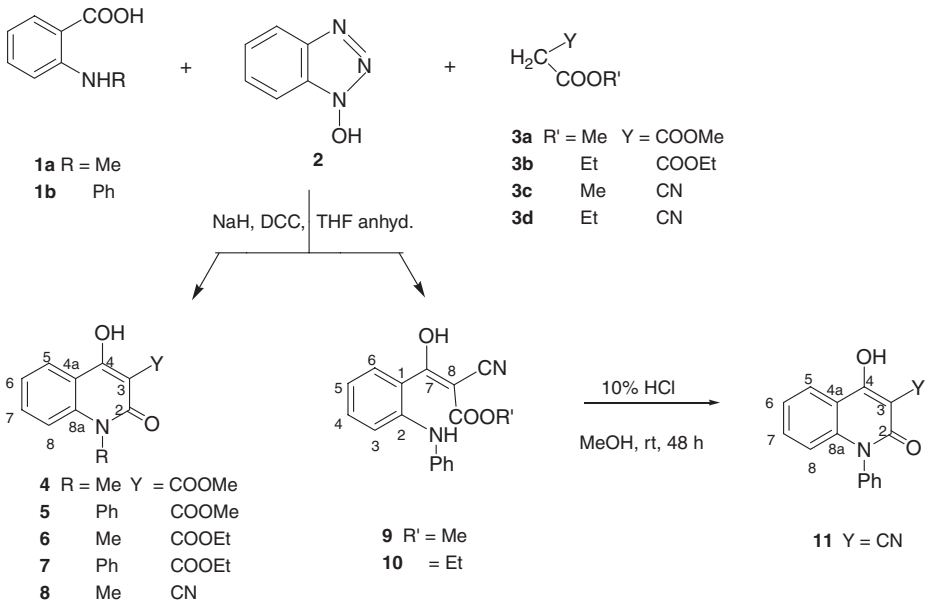

Scheme 1. Synthesis of 3-substituted 4-hydroxy-1-methyl- and 1-phenyl-2-quinolones.

2-quinolones **4**–**7**, as was expected. However, with cyanoacetates **3c** and **3d**, an alternative route involves formation of the *C*-acylation functionalized "intermediates" (**9** and **10**) or 3-cyano-4-hydroxy-1-methyl-2-quinolone (**8**) depending on the substituent of the nitrogen of the anthranilic acid. The closing of the heterocyclic ring of the β-3-(2-anilinophenyl)-2-cyano-3-hydroxypropenoates **9** and **10** is achieved by treatment with HCl (10%) in methanol to the desired 3-cyano-4-hydroxy-1-phenyl-2-quinolone.

We can therefore assume that the inductive effect of the group attached to the nitrogen atom plays the most important role on the derivative produced when cyanoacetates are used as the active methylene compounds. When the group is a methyl, characterized by a +I inductive effect, the heterocyclic ring-closure takes place spontaneously under the reaction conditions, and the intermediate *C*-acylation compound is not isolated. On the other hand, when a phenyl group, characterized by a −I inductive effect, is attached to *N*-1, the *C*-acylation compound is isolated, and the cyclization reaction is effected when this derivative is stirred in a mild acidic solution (10% hydrochloric acid in methanol).

The results from the ^{1}H and ^{13}C NMR chemical shifts, compared with previous spectral data,[21b,26] indicated the enolic form as predominant for the 4-hydroxy-2-quinolinones (**4**–**8**, **11**) and the *C*-acylation product **10**. However, the ^{1}H NMR spectrum of methyl 3-(2-anilinophenyl)-2-cyano-3-hydroxypropenoate (**9**) exhibited two tautomers, the enolic and the keto form (see Experimental). The assignments of the ^{13}C NMR spectra were based on HECTOR experiments, effected by our laboratory for "quinolone" analogues in the past.[21b,22,27,28]

An important feature of the proposed methodology has been the use of 1-hydroxybenzotriazole ester as a useful precursor for the synthesis of compounds with interesting biological properties. The activation of *N*-alkylanthranilic acid as its hydroxybenzotriazole ester, without any protection on the amine group, is an attractive alternative to other activated anthranilic acid species, permitting mild reaction conditions. Another advantage is that there is no need for isolating the intermediate active ester. This fact reduces the reaction time, in contrast to previously described methodologies, and is beneficial for the overall yield of the reaction. Additionally, the methodology is simple, inexpensive and easily scaled up.

Moreover, the 1-hydroxybenzotriazole is a powerful acylating agent, bearing no other active sites on its molecule. We could therefore apply stronger bases (e.g., LDA) without the fear of side reactions and by-products.

In conclusion, the synthesis of a series of 3-substituted 4-hydroxy-2-quinolones has been achieved through a one-step methodology, utilizing 1-hydroxybenzotriazole esters of *N*-methyl- and *N*-phenylanthranilic acid as acylating agents of appropriate active methylene compounds. The reaction gives high yields and has a short reaction time in contrast to previous methodologies. Work currently in progress includes application of the proposed methodology to the preparation of other quinolone derivatives bearing different functional groups at position 3 and the aromatic nucleus. Also, the application of this methodology in the synthesis of natural products containing the quinolone nucleus is in our near future plans.

Experimental

Melting points were determined on a Galenkamp MFB-595 melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna IR 560. NMR spectra were recorded on a Varian Gemini 2000, 300 MHz spectrometer. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). *J* values are given in Hz. Elemental analyses were recorded on a Euro EA3000 Series Euro Vector CHNS Elemental Analyser.

General Procedure for the Synthesis of 3-Substituted 4-Hydroxy-2-quinolones. To a solution of anthranilic acid (**1**) (10 mmol) and 1-hydroxybenzotriazole (**2**) (10 mmol) in anhydrous tetrahydrofuran (40 mL) was added dropwise a solution of dicyclohexylcarbodiimide (DCC) (10 mmol) in anhydrous tetrahydrofuran (5–10 mL) at 0 °C over the course of 1 h. The resulting

suspension was kept overnight at 3–5 °C. The precipitated solid (DCU) was filtered off and the filtrate was added to a solution of the anion of the appropriate active methylene compound [generated from sodium hydride (20 mmol) and **3a**–**3d** (10 mmol) in anhydrous tetrahydrofuran (60 mL)]. The resulted mixture was stirred at r.t. for 2.5 h and then concentrated in vacuo. The obtained gummy solid was dissolved with water and washed with diethyl ether. The aqueous extract was acidified with 10% hydrochloric acid in an ice water bath. The precipitated white solid (1-hydroxybenzotriazole) was filtered off, washed with dichloromethane and the combined aqueous and organic filtrate was extracted with DCM (3 × 15 mL). The combined organic extracts were dried with Na_2SO_4, filtered and concentrated in vacuo to afford either the 3-substituted 4-hydroxy-1-methyl- and 1-phenyl-2-quinolones **4**–**8** as white solids or the *C*-acylation compounds **9** and **10** as oily products. The solid products were collected by filtration, washed with light petroleum and dried in vacuo. The *C*-acylation compounds **9** and **10** (5 mmol) were dissolved in 10 mL methanol and treated with 10 mL 10% hydrochloric acid. The resulting mixture was stirred at r.t. for 48 h to afford the 3-cyano-2-quinolone (**11**) as solid product which was collected by filtration, washed with diethyl ether, and dried in vacuo.

Compound Spectroscopic and Analytical Data. Methyl 4-Hydroxy-1-methyl-2(1*H*)-oxoquinoline-3-carboxylate (4): 1.5 g, 64% yield; mp 163–164 °C; (lit.[29] 166–167 °C); IR (KBr) 1652 (CO ester), 1624 (CO amide), 1561 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (3H, s, N-CH_3), 4.03 (3H, s, $COOCH_3$), 7.24–7.33 (2H, m, H-6/H-8), 7.69 (1H, pt, H-7), 8.18 (1H, dd, $J = 8.0/1.4$, H-5), 14.07 (1H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 29.1 (N-CH_3), 52.9 ($COOCH_3$), 97.8 (C-3), 114.2 (C-4a), 114.9 (C-8), 122.1 (C-6), 125.8 (C-5), 134.6 (C-7), 141.4 (C-8a), 159.8 (C-2), 171.8 (C-4), 173.2 ($COOCH_3$).

Methyl 4-Hydroxy-2(1*H*)-oxo-1-phenylquinoline-3-carboxylate (5): 2.1 g, 55% yield; mp 172–173 °C; IR (KBr) 1678 (CO ester), 1619 (CO amide), 1558 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (3H, s, $COOCH_3$), 6.61 (1H, d, $J = 8.4$, H-8), 7.20–7.60 (7H, m, aromatic protons), 8.20 (1H, dd, $J = 8.2/1.5$, H-5), 14.27 (1H, s, OH); ^{13}C NMR ($CDCl_3$) δ 52.8 ($COOCH_3$), 97.9 (C-3), 114.6 (C-4a), 116.0 (C-8), 122.2 (C-6), 125.4 (C-5), 128.8/129.2/130.1/137.5 (aromatic carbons), 134.1 (C-7), 142.3 (C-8a), 159.9 (C-2), 172.6 (C-4), 173.2 ($COOCH_3$). Anal. Found: C, 69.02; H, 4.29; N, 4.69%. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74%.

Ethyl 4-Hydroxy-1-methyl-2(1*H*)-oxoquinoline-3-carboxylate (6): 1.5 g, 61% yield; mp 101–102 °C (lit.[19,20] 100–102 °C); IR (KBr) 1657 (CO ester), 1628 (CO amide), 1562 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (3H, t, $J = 7.2$, $COOCH_2CH_3$), 3.65 (3H, s, N-CH_3), 4.50 (2H, q, $J = 7.2$, $COOCH_2CH_3$), 7.23–7.33 (2H, m, H-6/H-8), 7.68 (1H, pt, H-7), 8.18 (1H, dd, $J = 8.0/1.4$, H-5), 14.21 (1H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 14.1 ($COOCH_2CH_3$), 29.1 (N-CH_3), 62.3 ($COOCH_2CH_3$), 98.0 (C-3), 114.2 (C-4a), 115.0 (C-8), 122.0 (C-6), 125.8 (C-5), 134.5 (C-7), 141.4 (C-8a), 159.8 (C-2), 171.9 (C-4), 172.8 ($COOCH_2CH_3$).

Ethyl 4-Hydroxy-2(1*H*)-oxo-1-phenylquinoline-3-carboxylate (7): 1.7 g, 56% yield; mp 177–178 °C (lit.[19] 180–183 °C); IR (KBr) 1677 (CO ester), 1622 (CO amide), 1558 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (3H, t, $J = 7.2$, $COOCH_2CH_3$), 4.46 (2H, q, $J = 7.2$, $COOCH_2CH_3$), 6.58 (1H, d, $J = 8.7$, H-8), 7.20–7.27 (3H, m, aromatic protons), 7.41–7.60 (4H, m, aromatic protons), 8.20 (1H, dd, $J = 8.0/1.4$, H-5), 14.45 (1H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 14.0 ($COOCH_2CH_3$), 62.3 ($COOCH_2CH_3$), 98.1 (C-3), 114.7 (C-4a), 116.0 (C-8), 122.2 (C-6), 125.4 (C-5), 128.9/129.3/130.2/137.6 (aromatic carbons), 134.0 (C-7), 142.4 (C-8a), 159.9 (C-2), 172.7 (C-4), 172.9 ($COOCH_2CH_3$).

3-Cyano-4-hydroxy-1-methyl-2-quinolone (8): 1.2 g, 60% yield; mp 300–301 °C (lit.[19] 290–293 °C); IR (KBr) 2227 (CN), 1620 (CO), 1590 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.55 (3H, s, N-CH_3), 7.32 (1H, pt, H-6), 7.54 (1H, d, $J = 8.7$, H-8), 7.76 (1H, pt, $J = 7.5$, H-7), 8.10 (1H, d, $J = 7.8$, H-5); ^{13}C NMR (DMSO-d_6) δ 29.2 (N-CH_3), 86.2 (C-3), 115.0 (C-4a), 115.4 (C-8), 115.5 (CN), 122.3 (C-6), 124.7 (C-5), 134.3 (C-7), 140.7 (C-8a), 160.5 (C-2), 168.6 (C-4).

Methyl 3-(2-Anilinophenyl)-2-cyano-3-hydroxypropenoate (9): 2.0 g, 75% yield; mp 80–82 °C (precipitated as yellow solid after several extractions of the oily product with pentene); ^1H NMR ($CDCl_3$) δ 3.95 (3H, s, $COOCH_3$), 5.30 (0.3H, s, methine proton keto), 6.90–7.38 (9H, m, aromatic protons and NH), 7.69 (1H, dd, $J = 7.6/1.5$, H-5), 14.57 (0.7H, s, OH); ^{13}C NMR ($CDCl_3$) δ 53.4 ($COOCH_3$), 81.2 (*C*CN), 113.9 (CN), 115.4/117.3/119.6/123.0/129.5/130.9/131.8/132.9/133.9/134.3/141.2/143.9 (aromatic carbons), 171.9 ($COOCH_3$), 184.5 (*C*=CCN). Anal. Found: C, 69.12; H, 4.56; N, 9.50%. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52%.

Ethyl 3-(2-Anilinophenyl)-2-cyano-3-hydroxypropenoate (10): 2.1 g, 76% yield (oily product); ^1H NMR ($CDCl_3$) δ 1.40 (3H, t, $J = 7.2$, $COOCH_2CH_3$), 4.40 (2H, q, $J = 7.2$, $COOCH_2CH_3$), 6.92–7.38 (9H, m, aromatic protons and NH), 7.68 (1H, dd, $J = 8.0/1.4$, H-5); ^{13}C NMR ($CDCl_3$) δ 14.4 ($COOCH_2CH_3$), 63.3 ($COOCH_2CH_3$), 81.1 (*C*CN), 115.7 (CN), 117.6/119.8/120.7/122.5/123.1/129.4/129.7/131.1/132.0/134.0/141.7/144.0 (aromatic carbons), 171.7 ($COOCH_2CH_3$), 184.8 (*C*=CN).

3-Cyano-4-hydroxy-1-phenyl-2-quinolone (11): 0.6 g, 51% yield, mp 290–291 °C; (lit.[30] 298–300 °C); IR (KBr) 2232 (CN), 1618 (CO), 1566 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.51 (1H, d, $J = 8.7$, H-8), 7.25–7.64 (7H, m, aromatic protons), 8.12 (1H, d, $J = 7.8$, H-5); ^{13}C NMR (DMSO-d_6) δ 86.1 (C-3), 113.9 (C-4a), 115.7 (CN), 116.0 (C-8), 122.3 (C-6), 124.7 (C-5), 129.0/129.5/130.2/137.3 (aromatic carbons), 133.8 (C-7), 141.7 (C-8a), 160.7 (C-2), 169.8 (C-4).

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