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52 *Current Microwave Chemistry,* 2014, *1*, 52-58

Microwave Assisted Synthesis of ethyl-quinolon-4-one-3-carboxylates and Hydrolysis to quinolon-4-one-3-carboxylic Acids

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Abstract: A fast and efficient microwave assisted synthesis of several ethyl-quinolon-4-one-3-carboxylates and quinolon-4-one-3-carboxylic acids has been developed. The 3-carboethoxy quinolones are easily obtained in a one-pot procedure through the cyclization of aminomethylenemalonate intermediates obtained by reaction of different *p*-substituted anilines and diethyl-ethoxymethylenmalonate. These quinolones are then irradiated under base hydrolysis conditions to get the carboxylic acids through a very fast and clean approach.

Keywords: Carboxylic acids, catalysis, cyclization, hydrolysis, malonates, microwave, open-vessel, quinolones, sealed-vessel, thermolysis.

INTRODUCTION

The quinolone structure is extensively used in a variety of pharmacologically active synthetic and natural compounds [1]. Among them, 4-quinolones derivatives are not only an important class of antibacterial [2], antidiabetic [3] and anticancer [4] agents but also a useful structural moiety for drug candidates [5].

All of these applications justify the effort to develop new efficient strategies to synthesize this structural moiety. However, existing synthetic methods for 3-substituted-quinol-4-ones usually require multistep processes and laborious isolation of the intermediates.

Nowadays a variety of synthetic methodologies to obtain heterocycles can be explored such as metal-catalyzed couplings [6], multicomponent reactions [7] and microwave-assisted synthesis [8]. These techniques, by themselves or in combination with others, make it possible to obtain better results in a more efficient and mild way.

In recent decades, microwave-assisted organic synthesis (MAOS) has gained an important role in organic and medicinal chemistry. Microwave heating can intensely accelerate a wide range of reactions, especially when they are carried out under solvent-free conditions [9]. Microwave irradiation allows the temperature to increase uniformly throughout the sample, which minimizes the presence of undesired by-products allowing a precise control of reaction conditions [10].

As part of our continuing effort to produce heterocycles *via* microwave assisted reactions, we set out to develop a rapid synthetic methodology for the generation of various quinolones [11,12].

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In this work we report an efficient microwave assisted synthesis of ethyl-quinolon-4-one-3-carboxylates using different anilines and diethyl-ethoxymethylenmalonate as starting materials. The classical synthesis of these 3-carboethoxy-quinolones usually requires many hours at reflux temperatures in high-boiling-point organic solvents [13]. Our experimental approach resulted advantageous and easy to carry out in few minutes using microwaves giving very good yields of the desired quinolones. In a second step the fast hydrolysis of quinolone esters was also achieved using microwave irradiation and base conditions giving carboxylic acids in excellent yields.

RESULTS AND DISCUSSION

The synthesis of ethyl-quinolon-4-one-3-carboxylates (**4**) consisted of a two-step sequence that involves the initial reaction between anilines (**1**) and diethyl-ethoxymethylen-malonate (**2**) to give diethyl 2-((phenylamino)methylene) malonate derivatives (**3**), which eliminate ethanol affording the quinolones by a cyclization reaction (Scheme **1**).

To carry out the reaction, an equimolar mixture of **1a-g** and **2** was initially exposed to microwave irradiation at 80 ºC for 1 min in solvent-less conditions using a closed system (Step 1, Scheme **1**). Quantitative formation (> 95 %) of diethyl malonates **3a-g** was established by ^{1}H-NMR analysis of the reaction mixture. These products were in excellent purity conditions to be used in the next step without isolation. It should be noted that the solvent-free preparation of **3b** using microwaves was already reported in the literature (2 min, 70 ºC, 97 % yield); however, in this report we have expanded the scope of this chemistry to other malonate derivatives synthesis obtaining excellent yields [14, 15].

To optimize the reaction conditions of cyclization of diethyl malonates **3** towards quinolones **4** (Step 2, Scheme **1**), **3a** was selected as model reactant to perform the reaction.

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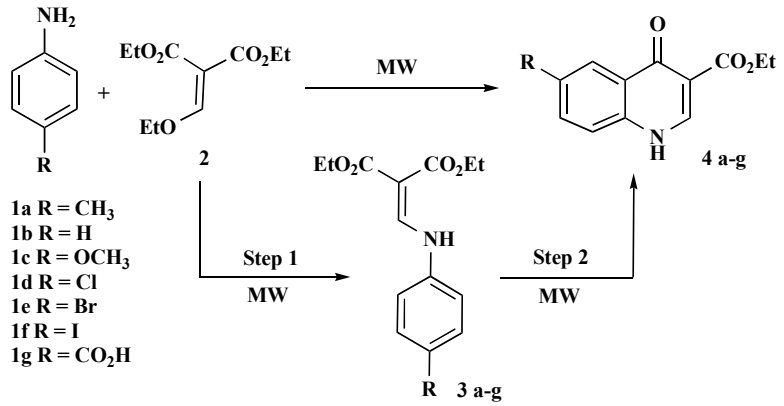


Scheme 1. Synthesis of ethyl-quinolon-4-one-3-carboxylates **4**.

We started with sealed vessel reactions because they are safer and easier to perform than open systems. As a first attempt, solvent-free reaction of **3a** was performed in a closed vessel. After microwave irradiation for several minutes using the maximum power irradiation (300 W) the temperature reached only 115 ºC, a low value considering that the required temperature for cyclization of malonates in conventional and microwave irradiated reactions should be higher than 220 ºC [13,15]. It is known that in the case of reactions involving low microwave absorption reagents and solvents, passive heating elements can be used to improve the microwave absorption as well as the heat transfer [16]. In this regard, we tried reactions using graphite (powder < 20 μm, ≥ 99.99 % purity) and silicon carbide (SiC, 200-450 mesh) as microwave susceptors. Using both additives, temperatures of reaction mixture were raised to 220-260 ºC depending on the irradiation time and amount of the absorber; however, yields of **4a** were still low (4-26 %, entries 1-5, Table **1**). In these heterogeneous experiments, open vessel reactions were also evaluated but this system did not promote any significant improvement. As an additional difficulty, total removal of graphite and SiC carbonaceous solids from the crude was hard and deficient mainly due to the insolubility of the quinolones in most common organic solvents.

To improve not only the microwave absorption of **3a** but also its cyclization reaction to **4a**, the presence of different catalysts, $Ce(NO_3)_3$, $BiVO_4$, bentonite, polyphosphoric acid (PPA) and Na_2CO_3 was also studied. It is known that cerium and bismuth catalyst have been applied as Lewis acid imparting high regioselectivity and chemoselectivity in various chemical processes [17]. Besides, PPA has been used as acid catalyst in the formation of several 4-quinolones [18] and *p*-chlorobenzoic acid was used in the microwave-assisted synthesis of sulfamoyl-4-oxo-quinolines [19]. Different clays were also used for solvent-free 'dry media' reactions [9, 20]. In other approaches base catalysts were evaluated in the microwave assisted synthesis of 2-aryl-4-quinolones [21]. In our case, temperatures reached up to 250 ºC for all catalyzed experiments of **3a** using sealed vessel systems; however, the synthesis of the desired quinolones did not proceed efficiently. Low yields of **4a** (< 15%) as well as high decomposition of starting material were observed.

After that, different solvents were evaluated for the reaction: water, acetonitrile, *N*,*N*-dimethylformamide (DMF), 1,2-dichlorobenzene (DCB) and diphenyl ether (DPE). In the case of reactions in water and acetonitrile, temperatures were not higher than 200 ºC and conversion of **3a** was depleted. When DMF was used, temperatures raised 250 ºC in 1 min at 300 W, giving only 10 % of **4a**. Interestingly, acceptable yields (29-49 %) were obtained when DCB and DPE were used as solvents. In both cases longer reaction times produced a decrease in the yields favoring the formation of undesired products [14]. Better results were achieved when **3a** was subjected to irradiation for 1 min in DCB at 250 ºC (entry 10, Table **1**) using a dynamic irradiation method, that is, a temperature-controlled method in which the variation of the power allowed us to reach a precise temperature value. Another irradiation method was also applied, in this case the power was fixed and the temperature oscillated within a range of ± 10 ºC (entries 7-9, 11-12 and 17).

In order to make a *'one-pot'* procedure, the solvent (DCB) was added to the mixture of **1a** and **2** from the beginning then, two consecutive irradiation steps were applied, the first one was 1 min at 80 ºC followed by 2-10 min at 250 ºC. Yields of **4a** were identical to those obtained in two independent steps (Scheme **1**), so we applied this methodology to the rest of the experiments. Additionally, the experimental protocol was very simple because quinolone **4a** was isolated in pure form by simple filtration and washing.

In our case, microwave-assisted reactions performed under sealed vessel conditions were not good enough to get high yields of **4a** or at least yields similar to that obtained by conventional synthesis (77 % at 250 ºC in DPE) [13]. Taking into account that one equivalent of ethanol is produced in each step of the reaction- which under atmospheric pressure conditions can be easily removed- we decided to apply microwave irradiation under open vessel conditions. The experimental arrangement was designed to closely simulate the conventional oil bath synthesis, where yields of quinolones were very good [13] (Table **3**). Thus, a conical bottom flask was placed inside the cavity and was fitted with a quartz column adapter (See Supporting Information). A standard distillation kit was attached to the top of the column which, in some cases, was connected to a round bottom flask immersed in liquid air.

Different tests in open vessel indicated that ethanol should be released for shifting the equilibrium towards products. As shown in Table **1**, open vessel reactions (using DFE) resulted in better yields of quinolone than closed ves-

Table 1. Microwave conditions for the synthesis of quinolone 4a.

Entry	Solvent	Additive	Reactor[a]	Power (W)	Time (min)	Temp. (ºC)[b]	Yield (%)[c]
1	-	CSi[d]	Sealed	100-200	10	220 (223)	7
2	-	CSi[d]	Sealed	25-175	2	260 (268)	26
3	-	CSi[e]	Open	100-300	5	250 (258)	23
4	-	Graphite[f]	Sealed	50-250	2	250 (253)	-
5	-	Graphite[f]	Open	175-300	2	250 (255)	9
6	DPE	-	Sealed	150-300	1	250 (252)	20
7	DPE	-	Sealed	100	5	260±10	23
8	DPE	-	Sealed	200	5	260±10	34
9	DPE	-	Sealed	300	5	260±10	32
10	DCB	-	Sealed	100-250	1	250 (255)	49
11	DCB	-	Sealed	200	5	260±10	33
12	DCB	-	Sealed	200	10	260±10	44
13	DPE	-	Open	50-300	5	250 (253)	57
14	DPE	-	Open	275-300	2	250 (252)	41
15	DPE	-	Open	200-300	2	250 (251)	67[g]
16	DPE	-	Open	150-300	1	260 (261)	55[g]
17	DPE	-	Open	200	4	260±10	57[h]

[a]Vessel of 10 mL was used in closed systems while 25 mL flask was used in open system. [b]In parentheses, maximum temperature reached. [c]Yields of isolated product calculated from anilines. [d]Molar ratio 1a: CSi was 12:1. [e]Molar ratio 1a: CSi was 18:1. [f]Molar Ratio 1a: Graphite was 11:1. [g]Collection receiver immersed in a liquid air bath. [h]Experiments carried out under air flow.

sel experiments. Although DCB was a good solvent under sealed vessel conditions, temperature was not higher than 180 ºC in the open vessel conditions and starting **3a** was obtained without any change.

It is important to highlight that the reaction performed with the flask connected to the end of the refrigerant immersed in liquid air resulted in higher yields of product. Evidently, the temperature difference between the reaction vessel and the flask outside the reactor pushed the volatile ethanol out. A similar effect was expected in reactions performed in air flow. However, this condition did not substantially improve the yields of **4a**. Also, irradiation times longer than 4 min did not improve the yields of quinolones and DPE decomposed forming undesirable products.

Up to this point, the best condition was the irradiation of **3a** at 250 ºC for 2 min using dynamic irradiation method (entry 15, Table **1**).

After that, the cyclization of malonates **3b-g** was carried out applying the enhanced conditions acquired in open vessel as well as in sealed vessel experiments of **3a**. These results are depicted in Table **2**. It was clear that the synthesis of quinolones was favored under open vessel conditions. These findings were attributed to the fact that ethanol can be easily released promoting the reaction along the desired pathway, as it was observed in other reactions [22].

For open systems, in some cases, reaction temperatures of 250 ºC gave high amount of quinolones, but the products were very impure. Therefore, optimal temperature for the synthesis of quinolones **4a-g** was found to be 240 ºC.

Furthermore, yields of **4a-g** were improved when an excess of **2** (molar ratio **1**: **2** equal to 0.5) was used. This behavior was also observed by Lange *et al.* in the microwave assisted synthesis of 3-aryl-4-hydroxyquinolin-2-ones [23]. Thus, optimal conditions for the synthesis of quinolones using DPE as solvent were found to be: 1 min of microwave irradiation at 80 ºC under open vessel conditions followed by 2 min of irradiation under the variable power method at 240 ºC. These conditions allowed us to obtain **4a-g** in excellent yields, even better than preparations involving conventional heating (Table **3**). The conventional synthesis of compounds **4a-c** and **4e** was carried out previously in our research group [13] and we added two new compounds, **4d** and **4f-g** to our library of quinolones.

In order to expand our library of quinolones we studied the hydrolysis of ethyl quinolone-carboxylates to afford quinolone carboxylic acids. The 4-quinolone-3-carboxylic acid derivatives are widely known for their use as antibacterial agents. Additionally, these types of compounds are an attractive scaffold in medicinal chemistry to obtain many quinolone derivatives, as amides which are a promising class of compounds displaying interesting biological activity as anti-

Table 2. Yields of quinolones 4 a-f in open and sealed microwave experiments.

Compound	R	Yield (%)[a]				
		Open System[b]				Sealed System[c]
		220 ºC	230 ºC	240 ºC	250 ºC	(260± 10) ºC
4a	CH_3	10	34	66	67	49[d]
4b	H	25	58	75	62	32
4c	OCH_3	13	48	54	55	30
4d	Cl	4	36	80	82	44
4e	Br	12	70	65	46	57
4f	I	19	23	67	85	59

[a]Yields of isolated product, values calculated from starting anilines. Molar ratio **1**: **2** equal to 1. [b]Solvent: DPE, irradiation time: 3 min. [c]Solvent: DCB, irradiation time: 6 min. [d]Temperature: 250-255 ºC, irradiation time: 2 min.

Table 3. Microwave vs. conventional synthesis of quinolones 4.

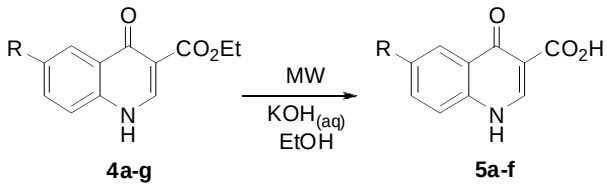
R	Microwave Method[a]	Conventional Method	
	Yield (%)	Time (h)	Yield (%)[c]
CH_3	79 [b] (74)[c]	1	77
H	75 [b] (68)[c]	1	31
OCH_3	68 [b] (65)[c]	0.75	58
Cl	87 [b] (82)[c]	3	71
Br	91 [b] (83)[c]	5	71
I	89 [b] (87)[c]	3	63
CO_2H	80 [b] (71)[c]	1	63

[a]Molar ratio **1**: **2** equal to 0.5, irradiation time: 3 min. [b]Isolated product. [c]Recrystallzed from DMF.

HIV agents [24] or as cannabinoid ligands, [25] among others [26].

The formation of carboxylic acids from ethyl quinolonecarboxylates is carried out under base and acid conditions and usually takes long reaction times at temperatures of solvent reflux [26]. In order to simplify the methodology, microwave irradiation was applied to achieve the hydrolysis of quinolones **4a-g**. Therefore, a mixture of carboethoxy quinolones and aqueous KOH (10% w/v) in ethanol was irradiated at 90-100 ºC for 15 min. After cooling, the mixture was acidified with concentrated HCl to get corresponding acids (see Table **4**). Compounds **5a-f** were obtained in excellent yields and hydrolysis of ester derivatives was successful; however, for compound **4g** the corresponding acid (**5g**) was not detected under any experimental condition producing mainly decomposition products. This fact can be attributed to the possible instability of the dicarboxylic acid product, which can suffer other transformations under the microwave heating conditions.

Table 4. Hydrolysis of quinolones 4 in basic media.



4a-g **5a-f**

Compound	R	Yield %[a]
5a	CH_3	97
5b	H	95
5c	OCH_3	81
5d	Cl	90
5e	Br	86
5f	I	82
5g	CO_2H	ND[b]

[a]Isolated compound. [b]Not detected in the reaction mixture.

CONCLUSION

In this work we applied microwave irradiation to optimize the preparation of various ethyl-quinolon-4-one-3-carboxylates and from these compounds the corresponding carboxylic acids in an easy and efficient protocol. At this point it is important to highlight that microwave heating reduced the reaction times for synthesis of all quinolones from

hours to minutes improving in most of the cases the yields obtained in conventional synthesis.

MATERIALS AND METHODS

(1) General Method

All organic starting materials were analytically pure and used without further purification. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra of aminomethylenmalonates **3a-g** and quinolones **4g** and **5a-f** were recorded on a Bruker Advance II 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) using DMSO-d_6, TFA-d_1 and D_2O as solvents. The spectra of aminomethylenmalonates were identical to the previously reported [13]. ^{1}H and ^{13}C NMR spectra of quinolones **4a-f** were recorded on INOVA 600 MHz Varian (^{1}H at 600 MHz and ^{13}C at 150.9 MHz) using $(CD_3)_2SO$ as solvent. Chemical shifts (δ) were referenced to TMS, and ^{13}C-NMR chemical shifts (δ) were referenced to internal solvent resonance.

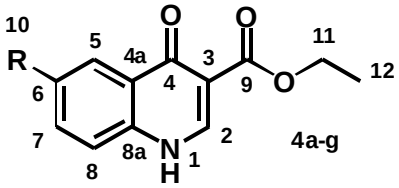
(2) General Procedure for the Synthesis of the ethyl-quinolon-4-one-3-carboxylates (4a-g)

In a typical ¨one pot¨ experiment a mixture of 0.25 g (2.68 - 1.14 mmol) of aniline **1a-g**, diethyl-ethoxymethylenmalonate (1.08 – 0.46 mL) and DPE (2 mL) was irradiated with two consecutive methods. The first one was 1 min at 80 °C followed by 2 min at 240 °C using an open vessel (see supplementary information) to afford derivatives **4a-g**. These quinolones were precipitated in hexane (10 mL), the solids were collected by filtration, washed with acetone, dried, and recrystallized from DMF. The yields of **4a-g** were calculated from starting anilines **1a-g**.

(3) General Procedure for the Synthesis of the quinolon-4-one-3-carboxylic acids (5a-f)

A mixture of 0.25 g (1.15-0.73 mmol) carboethoxy quinolones (**4a-f**), 2 mL of aqueous solution of KOH (10% w/v) and 2 mL of ethanol was irradiated at 90-100 ºC during 15 min using an open vessel system. After cooling, the mixture was acidified with HCl (1M) to get the corresponding acids. Finally, the solids were collected by filtration, washed with water and dried.

(4) Characterization Data of Products



4a-g

ethyl-6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (4a): White solid, m.p. >280ºC decomposes. ^{1}H NMR (600 MHz, DMSO-d_6): $\delta_{(ppm)}$ 1.28 (t, 3H$_{12}$, J= 7.1 Hz); 2.42 (s, 3H$_{10}$); 4.21 (q, 2H$_{11}$, J= 7.1 Hz); 7.51 (dd, 1H$_8$, J= 8.2 and 0.7 Hz); 7.53 (dd, 1H$_7$, J= 8.2 and 1.8 Hz); 7.95 (s, 1H$_5$); 8.49 (d, 1H$_2$, J= 6.7 Hz); 12.24 (d, 1H$_1$, J= 6.7Hz). ^{13}C NMR (100MHz, DMSO-d_6): $\delta_{(ppm)}$ 14.32; 20.77; 50.44; 109.46; 118.64; 124.91; 127.17; 133.58; 134.12; 136.91; 144.33; 164.81; 173.23.

ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (4b). White solid, m.p. >250ºC decomposes. ^{1}H NMR (600 MHz, DMSO-d_6): $\delta_{(ppm)}$ 1.28 (t, 3H$_{12}$, J= 7.1 Hz); 4.21 (q, 2H$_{11}$, J= 7.1); 7.41 (ddd, 1H$_6$, J=8.1, 7.0 and 1.1 Hz); 7.61 (ddd, 1H$_8$, J= 8.3, 1.1 and 0.6 Hz); 7.70 (ddd, 1H$_7$, J= 8.3, 7.0 and 1.5 Hz); 8.15 (ddd, 1H$_5$, J= 8.1, 1.5 and 0.7 Hz); 8.54 (d, 1H$_2$, J= 6.7 Hz); 12.30 (dd, 1H$_1$, J= 6.7 and 0.7 Hz). ^{13}C NMR (DMSO-d_6): $\delta_{(ppm)}$ 14.31; 59.52; 109.77; 118.73; 124.64; 125.59; 127.23; 132.35; 138.92; 144.83; 164.77; 173.38.

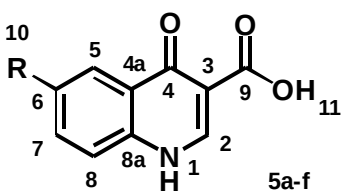
ethyl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (4c). Light brown solid, m.p. >280ºC decompose. ^{1}H NMR (600 MHz, DMSO-d_6): $\delta_{(ppm)}$ 1.28 (t, 3H$_{12}$, J= 7.1 Hz); 3.89 (s, 3H$_{10}$); 4.21 (q, 2H$_{11}$, J= 7.1 Hz); 7.34 (dd, 1H$_7$, J= 8.9 and 3.0 Hz); 7.57 (d, 1H$_5$, J= 3.0 Hz); 7.58 (d, 1H$_8$, J= 8.9 Hz); 8.49 (d, 1H$_2$, J= 6.7 Hz); 12.30 (dd, 1H$_1$, J= 6.7 Hz). ^{13}C NMR (DMSO-d_6): $\delta_{(ppm)}$ 14.31; 55.42; 59.44; 105.50; 106.63; 120.48; 122.14; 128.48; 133.29; 143.58; 156.55; 164.91; 172.81.

ethyl-6-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (4d).White solid, m.p.>280ºC decomposes. ^{1}H NMR (600 MHz, DMSO-d_6): $\delta_{(ppm)}$ 1.28 (t, 3H$_{12}$, J= 7.1 Hz); 4.21 (q, 2H$_{11}$, J= 7.1 Hz); 7.67 (d, 1H$_8$, J= 8.8 Hz); 7.76 (dd, 1H$_7$, J= 8.8 and 2.4 Hz); 8.08 (d, 1H$_5$, J= 2.4 Hz); 8.58 (d, 1H$_2$, J= 6.6 Hz); 12.5 (d, 1H$_1$, J= 6.6 Hz). ^{13}C NMR (DMSO-d_6): $\delta_{(ppm)}$: 17.29; 59.68; 110.03; 121.24; 124.58; 128.34; 129.34; 132.45; 137.66; 145.19; 164.53; 172.16.

ethyl-6-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylate (4e). White solid m.p.>300ºC decomposes. ^{1}H NMR (600 MHz, DMSO-d_6): $\delta_{(ppm)}$ 1.28 (t, 3H$_{12}$, J= 7.1 Hz); 4.22 (q, 2H$_{11}$, J= 7.1 Hz); 7.60 (d, 1H$_8$, J= 8.8 Hz); 7.86 (dd, 1H$_7$, J= 8.8 and 2.3 Hz); 8.22 (d, 1H$_5$, J= 2.3 Hz); 8.59 (s, 1H$_2$); 12.5 (s, 1H$_1$). ^{13}C NMR (100 MHz, TFA): $\delta_{(ppm)}$ 14.43; 67.22; 107.83; 123.49; 123.67; 127.42; 129.46; 140.44; 143.61; 147.53; 169.71; 174.89.

ethyl-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate (4f). White solid, m.p. >280ºC decomposes. ^{1}H NMR (600 MHz, DMSO-d_6): $\delta_{(ppm)}$1.28 (t, 3H$_{12}$, J= 7.1 Hz); 4.21 (q, 2H$_{11}$, J= 7.1 Hz); 7.44 (d, 1H$_8$, J= 8.7 Hz); 7.99 (dd, 1H$_7$, J= 8.7 and 2.2 Hz); 8.42 (d, 1H$_5$, J= 2.2 Hz); 8.57 (d, 1H$_2$, J= 6.7 Hz); 12.40 (d, 1H$_1$, J= 6.7 Hz). ^{13}C NMR (DMSO-d_6): $\delta_{(ppm)}$ 14.29; 59.67; 89.62; 110.28; 121.17; 128.90; 134.06; 138.30; 140.47; 145.16; 164.51; 171.94.

3-(ethoxycarbonyl)-4-oxo-1,4-dihydroquinoline-6-carboxylic acid (4g). Beige solid, m.p.: >280ºC decompose. ^{1}H NMR (400 MHz, TFA): $\delta_{(ppm)}$: 0.81 (t, 3H$_{12}$, J= 7.2 Hz); 3.98 (q, 2H$_{11}$, J= 7.16 Hz); 7.56 (d, 1H$_8$, J= 8.9 Hz); 8.13 (d, 1H$_7$, J= 8.8 Hz); 8.71 (s, 1H$_5$); 8.75 (s, 1H$_2$). ^{13}C NMR (TFA) $\delta_{(ppm)}$: 9.61; 62.58; 103.45; 117.39; 118.54; 125.86; 127.84; 134.85; 139.41; 144.71; 164.78; 166.72; 172.01.



5a-f

6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5a): White solid, hygroscopic. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta_{(ppm)}$ 2.49 (s, 3H$_{10}$); 7.73 (s, 1H$_8$); 7.74 (s, 1H$_7$);

8.10 (s, 1H$_5$); 8.86 (s, 1H$_2$); 13.39 (s, 1H$_1$); 15.49 (s, 1H$_{11}$). ^{13}C NMR (DMSO-d_6) δ (ppm) 21.27; 117.87; 119.95; 124.57; 124.79; 135.77; 136.48; 138.02; 144.87; 166.96; 178.53.

4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5b). White solid, hygroscopic. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 7.33 (ddd, 1H$_6$, *J*=7.9, 7.5 and 1.1 Hz); 7.56 (ddd, 1H$_8$, *J*= 7.7, 7.5 and 1.4 Hz); 7.65 (d, 1H$_7$, *J*= 8.2, broad signal); 8.16 (dd, 1H$_5$, *J*= 8.2 and 1.2 Hz, broad signal); 8.47 (s, 1H$_2$). ^{13}C NMR (D_2O): δ (ppm) 117.93; 123.50; 124.51; 126.23; 127.40; 130.06; 148.92; 152.29; 172.40; 177.08.

6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5c). White solid, hygroscopic. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.90 (s, 3H$_{10}$); 7.51 (dd, 1H$_7$, *J*= 2.9 and 9.1 Hz); 7.63 (d, 1H$_5$, *J*= 2.9 Hz); 7.77 (d, 1H$_8$, *J*= 9.0 Hz); 8.81 (s, 1H$_2$); 13.40 (s, 1H$_1$); 15.53 (s, 1H$_{11}$). ^{13}C NMR (DMSO-d_6): δ (ppm) 56.17; 104.64; 107.37; 121.89; 124.86; 126.14; 134.58; 143.86; 157.92; 167.05; 177.95.

6-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5d). White solid, hygroscopic. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.87 (d, 1H$_8$, *J*= 8.9 Hz); 7.91 (dd, 1H$_7$, *J*= 2.4 and 8.8 Hz); 8.18 (d, 1H$_5$, *J*= 2.2 Hz); 8.91 (s, 1H$_2$); 13.55 (s, 1H$_1$)14.97 (s, 1H$_{11}$). ^{13}C NMR (DMSO-d_6): δ (ppm) 108.46; 122.53; 124.42; 126.05; 131.30; 134.44; 138.61; 146.04; 166.42; 177.69.

6-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5e): White solid, hygroscopic. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.78 (d, 1H$_8$, *J*= 9.0 Hz); 8.04 (dd, 1H$_7$, *J*= 2.3 and 8.8 Hz); 8.36 (d, 1H$_5$, *J*= 2.2 Hz); 8.95 (s, 1H$_2$); 13.55 (s, 1H$_1$); 15.00 (s, 1H$_{11}$). ^{13}C NMR (DMSO-d_6): δ (ppm) 108.55; 119.41; 122.58; 126.37; 127.58; 137.05; 138.87; 146.08; 166.39; 177.58.

6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5f): White solid, hygroscopic. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.64 (d, 1H$_8$, *J*= 8.8 Hz); 8.17 (dd, 1H$_7$, *J*= 2.0 and 8.8 Hz); 8.56 (d, 1H$_5$, *J*= 1.8 Hz); 8.92 (s, 1H$_2$); 13.57 (s, 1H$_1$); 15.03 (s, 1H$_{11}$). ^{13}C NMR (DMSO-d_6): δ (ppm) 91.98; 108.59; 122.26; 126.57; 133.83; 139.21; 142.39; 145.82; 166.44; 177.43.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported financially by CONICET and SECyT-UNC. Thanks are given to Dr. Novruz Akhmedov (West Virginia University, USA) and Dr. Gloria Bonetto (University of Cordoba) for the good NMR experiments of quinolone compounds.

SUPPLEMENTARY MATERIAL

Description: Detailed experimental procedures and characterization analysis of products.

Supplementary material is available on the publishers Web site along with the published article.

ABBREVIATIONS

PPA	=	Polyphosphoric acid
DMF	=	*N*,*N*-Dimethylformamide
DCB	=	1,2-Dichlorobenzene
DPE	=	Diphenyl ether
TMS	=	Tetramethylsilane
DMSO	=	Dimethyl sulfoxide
TFA	=	Trifluoroacetic acid

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Received: February 13, 2014 Revised: March 30, 2014 Accepted: April 01, 2014