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SOLVENT-FREE SYNTHESIS OF QUINOLONE DERIVATIVES

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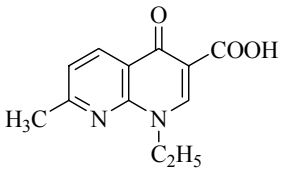
Dedicated to Professor Pierre Potier on the occasion of his 70th birthday.

Abstract – Quinolones can be prepared in a three step procedure from triethylorthoformate and activated methylene derivatives leading to alkoxymethylenemalonates followed by reaction with aromatic amines and finally a cyclization. All the reactions were carried out under solvent-free conditions possibly under microwave activation with benefits for the first step.

INTRODUCTION

Many compounds possessing a pyridone-3-carboxylic acid fragment have been synthesized and evaluated as potential antibacterial agents during the last half century.[1] First generation drugs , e.g. nalidixic acid **(1)** and oxolinic acid **(2)**, exhibit activity against most *Gram-negative* bacteria but they are inactive against *Pseudomonas aeruginosa* and *Gram-positive* bacteria.[2] Subsequent structural modifications have led to new analogues, second generation drugs, with improved antibacterial potency and activity against *P.aeruginosa.*[3] The third generation agents, like norfloxacin **(3)**, pefloxacin **(4)**, ciprofloxacin **(5)** and ofloxacin **(6),** which are 6-fluorinated compounds mostly with a piperazinyl substituent in position 7,[4] present greater activity against *Gram negative* bacteria including *P. aeruginosa* and high activity against most *Gram–positive* organisms.



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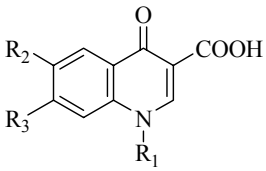
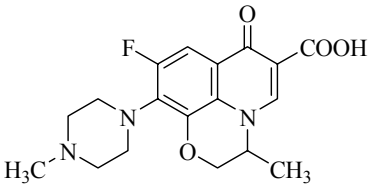


2 $R_1 = C_2H_5$, $R_2,R_3 = -CH_2-O-CH_2-$
3 $R_1 = C_2H_5$, $R_2 = F$, $R_3 = 1$-piperazinyl
4 $R_1 = C_2H_5$, $R_2 = F$, $R_3 = 4$-methyl-1-piperazinyl
5 $R_1 = $ cyclopropyl, $R_2 = F$, $R_3 = 1$-piperazinyl



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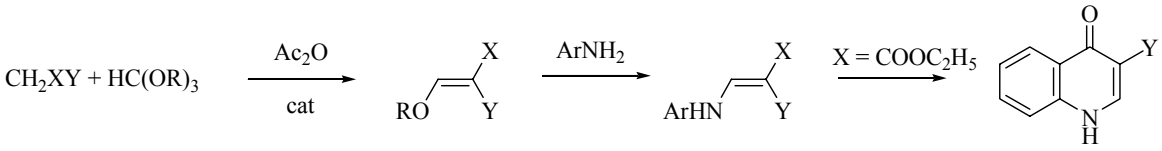
Scheme 1: Some characteristic quinolones derivatives

As already described in the literature, the 4-quinolone ring construction is generally realized by the Gould-Jacobs reaction.[5] This process includes the reaction between aromatic amines and alkoxymethylene compounds, followed by a thermal cyclization as shown in Scheme 2.[6] Starting alkoxymethylenemalonates are obviously prepared by condensation of trialkyl orthoformates with appropriate methylene components.



X, Y = $COOC_2H_5$, $COCH_3$, CN
R = alkyl
Ar = aryl

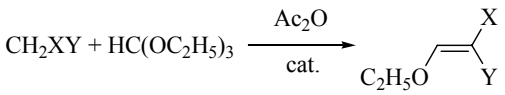
Scheme 2: Synthesis of quinolones derivatives

Nowadays, there is an increased interest for organic synthesis under clean and efficient solvent-free procedures and additionally, in adapted cases, activation by microwave (MW) irradiation.[7] The synthesis of several quinolones was already described using MW irradiation.[8] The solvent-free method is proved to be often more efficient than classical procedures and constitutes an evident simplification of workup and treatments within the frame of "Green Chemistry", as avoiding the use of added organic solvent during the reactions.[9] So we present here the solvent-free synthesis of quinolone derivatives bearing an electronwithdrawing group Y in position 3 (Scheme 2).

RESULTS AND DISCUSSION

Preparation of disubstituted alkoxymethylene derivatives (9)

Alkoxymethylene derivatives **(9)** were prepared by condensation of triethyl orthoformate **(8)** with activated methylene derivatives **(7)**[10] at 125°C using MW irradiation under accurately controlled conditions (monomode reactor with measurement and monitoring of pressure, emitted MW power and temperature). The influence of the presence of acetic anhydride and Brönsted acid (KSF montmorillonite) or Lewis catalyst ($ZnCl_2$) in the reaction was studied (Scheme 3).



7a-d **8** **9a-d**

a) X= Y = $COCH_3$, b) X= $COCH_3$, Y= $CO_2C_2H_5$, c) X= CN, Y = $CO_2C_2H_5$, d) X = Y = CN

Scheme 3: Synthesis of alkoxymethylene derivatives

The main results are given in Table 1.

Table 1: Condensation of triethyl orthoformate with activated methylene derivatives at 125 °C

Entry	Compound	**8:7:Ac_2O**	Cat	Time (min)	MW[a]		Δ[b]	
					Yield% **9**[c]	Conv. **7**[c]	Yield% **9**[c]	Conv. **7**[c]
1	**9a**	1.5:1:1	-	40	70	83	62	74
2		1.5:1:1.5	-	40	83	95	-	-
3		1.5:1:1	KSF	15	**61**	76	**38**	47
4	**9b**	1.5:1:1	-	105	78	82	82	86
5		1.5:1:1.5	-	105	89	90	-	-
6		1.5:1:1.	KSF	15	**64**	71	**44**	46
7	**9c**	1.5:1:1	-	120	**81**	85	**66**	77
8		1.5:1:1	KSF	120	75	83	74	85
9		1.5:1:1	$ZnCl_2$	60	78	80	76	77
10	**9d**	1.5:1:1	-	15	**93**	99	**68**	78

[a]Reactions were conducted in open vessels using a CEM monomode system.

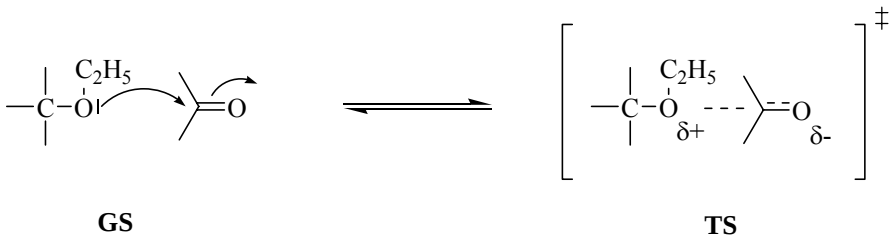
[b]Reactions were conducted under strictly identical conditions (same open vessels, *in situ* temperature followed by an optical fiber, mechanical stirring, etc...).

[c]Yields and conversions were determined by GC using an internal standard (ethyl benzoate or methyl benzoate).

The best results were obtained (Entries 2, 5, 7 and 10) when slight excesses of orthoester **(8)** and acetic anhydride were used (1.5 equiv.). The effect of acid catalyst (KSF or $ZnCl_2$) was not favorable.

In all the cases tested, a strict comparison of the results obtained by conventional heating (Δ) and MW activation under identical conditions was made (vessels, reaction time, temperature ramp). MW irradiation appears to be advantageous in the majority of cases (Entries 1, 3, 6, 7, 10) but to be ineffective in other examples (Entries 4, 8, 9).

This observation is consistent with mechanistic considerations as the mechanism involves the development of dipoles in the transition state and therefore an increase in the polarity of the system during the reaction progress starting from the ground state towards the transition state (Scheme 4), which induces a specific MW enhancement due to lowing in the activation energy (Figure 1).[11]



Scheme 4: Mechanism of condensation.

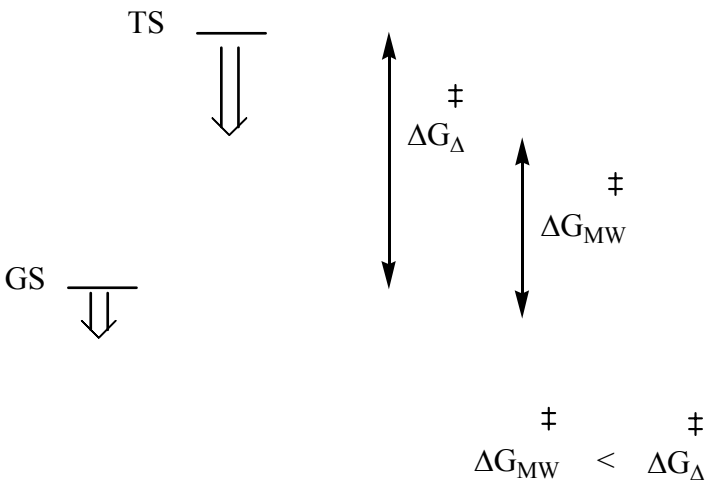


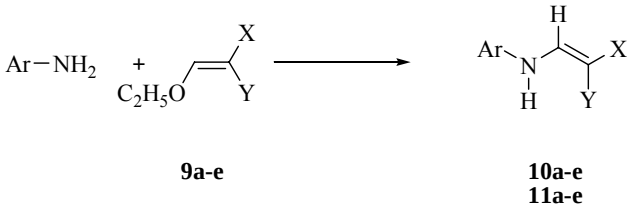
Figure 1: Relative stabilisation of ground (GS) and transition states (TS) by dipole-dipole interaction with electric field for a more polar TS.

Reaction of 9 with aromatic amines

Nitrogen nucleophiles are the most frequently ones used to displace alkoxy group and provide

aminoethylenemalonates which could be formally considered as aminoethylene derivatives with substituents in the β-position(s).[10a, 12]

We have applied the combination of solvent-free reaction and MW irradiation in order to prepare disubstituted aminomethylene derivatives (Scheme 5).



9a-e **10a-e** **11a-e**

a) X= Y = $COCH_3$, b) X= $COCH_3$, Y= $CO_2C_2H_5$, c) X= CN, Y = $CO_2C_2H_5$, d) X = Y = CN, e) X = Y = $CO_2C_2H_5$
10 $ArNH_2$ = aniline
11 $ArNH_2$ = 6-aminoquinoxaline

Scheme 5: Synthesis of aminomethylene derivatives

The main results are presented in Table 2.

Table 2: Solvent-free addition-elimination reaction between aniline (2 min, 70 °C) or aminoquinoxaline (10 min, 120 °C) and disubstituted alkoxymethylene derivatives

Compound	Yield of **10**(%)[a]	
	MW	**Δ**
10a	93	89
10b	96	98
10c	93	95
10d	95	94
10e	97	96
11a	91	92
11b	95	91
11c	82[b]	80[b]
11d	86[b]	87[b]
11e	91	92

[a] Isolated yield by flash chromatography

[b] Isolated yield by precipitation

Very good yields were obtained within very short reaction times. Comparable yields were obtained under

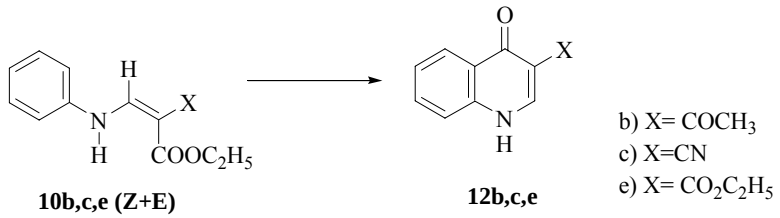
conventional heating and MW irradiation in the identical conditions. No MW specific effects were observed in this case and microwaves are only limited to purely thermal effects. This observation is consistent with the fact that this reaction is very easy (with a very low activation energy) with a reactant-like transition state. Therefore, the change in polarity of the system from the ground state to its transition state is rather limited, what is not in favor for the intervention of any specific MW effects.[11]

On another hand, when the reaction was performed more classically in refluxing ethanol or toluene for 1-6 h, 48-80% of the yields were obtained. This results proves that the solvent-free method is by far more suitable in this case.[9]

Intramolecular cyclization of 10 into 12

The Gould-Jacobs reaction[13] is a useful tool in organic synthesis to form antibacterial quinolone systems (Scheme 6). Generally, high boiling solvents such as biphenyl or diphenyl ether have been used for thermal processes which complicate workup and recovery.[14] To avoid this problem, a study of this reaction has been carried out under solvent-free conditions.

Firstly the thermal cyclizations of aminomethylenemalonates **(10b,c,e)** were performed under classical conditions in refluxing diphenyl ether. The cyclic products **(12b,c,e)** were obtained with satisfactory yields from starting materials, where at least one of the electron withdrawing groups is ethoxycarbonyl group[5] (Table 3).



10b,c,e (Z+E) **12b,c,e**

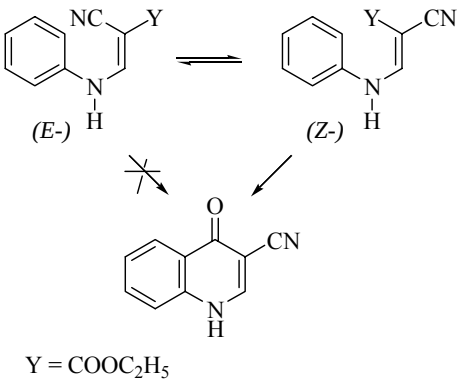
Scheme 6: Cyclization of aminomethylenemalonates into quinolones (Gould-Jacobs reaction)

Table 3 : Thermal cyclization of aminomethylenemalonates in diphenyl ether.

Entry	Compound	**10 (*E*/*Z*)**	Temperature (°C)	Time (h)	Yield % **12**[a]
1	**12b**	90/10	255	**1**	**65**
2	**12c**	75/25	255	3	45
3			265	**2**	**60**
4			265	3	40
5		30/70	265	**2**	**66**
6	**12e**	-	255	**0.75**	**80**

[a] Yield in isolated product obtained by precipitation

When considering the mechanism for cyclization,[15] we assume that only the isomer *Z* of compound **(10c)** can be cyclized and forms the desired product **(12c)** (Scheme 7). It was found that the isomerisation *E*→ *Z* of **(10c)** took place by increasing the time and the temperature. As demonstrated in Table 3 (see Entries 2-5), the initial proportion of two isomers of **10c** is not important in the thermal cyclization, presumably due to isomerisation occuring during the reaction conditions.



Scheme 7: Influence of isomer geometry in the cyclization of **(10c)**.

Further cyclization of **(10e)** (Y = $COOC_2H_5$) (Scheme 6) under solvent-free conditions either under MW irradiation or in a thermostatted metallic bath at the same temperature (250°C) was studied. Only 27% yields in **12e** was obtained whatever the mode of activation (conversions were 51 and 93% under MW and Δ respectively).

As already described in the literature,[14] the temperature was a critical point to minimize the decomposition in cyclized products. Next experiments were realized without solvent in a metallic bath at higher temperatures. Decreases in yields and important degradations were observed by extending reaction times. The profile of yields at different temperatures is shown in Figure 2.

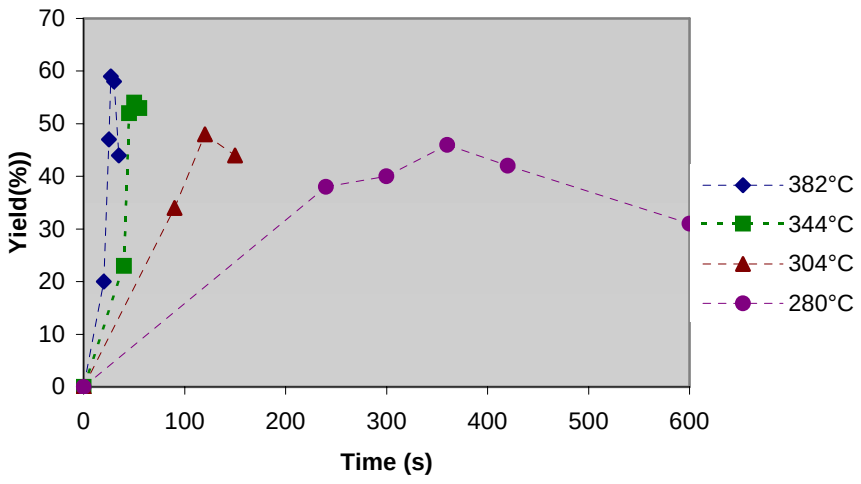


Figure 2: The profile of yields at different temperatures

The best result (60% yield) under solvent-free conditions was obtained at 380 °C for only 30 sec (Table 4). This yield is however lower than the one obtained when the reaction was performed in diphenyl ether (80% Entry 6 in Table 3). It is nevertheless of interest when one considers the simplicity of work-up when the use of high boiling solvent is avoided.

Table 4: Solvent-free thermal cyclization of diethyl phenylaminomethylenemalonate **(10e)** (380 °C, metallic bath)

Time (s)	Yield % **12e**[a]	Conversion % **10e**[b]
20	20	12
25	47	58
30	**60**	**82**
35	44	90

[a] Yield after precipitation

[b] Conversion determined by GC

CONCLUSIONS

In conclusion, we have developed a three step solvent-free procedure for the synthesis of quinolone derivatives. Non-thermal microwave specific effect was observed in the preparation of alkoxymethylenemalonates. It was also found that a slight excess of triethyl orthoformate improved the yield of this condensation. Aminomethylene derivatives were obtained in very good yields within short reaction times. Thermal cyclization of diethyl phenylaminomethylenemalonate was studied under solvent-free conditions and the results confirm that high temperatures and short reaction times are crucial to avoid the decomposition of generated product.

EXPERIMENTAL

Microwave experiments were conducted using monomode systems (focused waves thanks to a well-dimensionned wave guide):

CEM Discover Synthesis Unit operating at 2.45 GHz monitored by a PC computer. Waves are focussed by a circular wave-guide all round the cavity. Temperature was measured by optical fiber or IR detection with continuous feedback temperature control and maintained at a constant value by power modulation (0-300 W). Stirrring was provided with *in situ* magnetic variable speed stirrer when reactions were perfomed in closed vessels under controlled pressure or with a mechanical stirring in the case of reactions

in open vessels. Reactions were performed either in glass vessels (capacity 10 mL) sealed with a septum or in open vessels (capacity 100-250 mL). The pressure was controlled by a load cell connected to the vessels via a needle which penetrated just bellow the septum surface.

Prolabo-Synthewave 402 with focused waves operating at 2.45 GHz. The temperature was controlled all along the reaction and evaluated by an infrared detector which indicated the surface temperature (the IR detector was calibrated by tuning the emissivity factor using an optical fiber introduced into the reaction mixture). Temperature was maintained constant at a chosen value by modulation of emitted power. Mechanical stirring all along the irradiation provided a good homogeneity (power and temperature) and a data treatment which was followed by a computer. All reactions were performed in cylindrical Pyrex open vessels.

Melting points were measured with a Kofler bank. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6. ^{1}H NMR spectra were recorded at 200 or 250 MHz. Chemical shifts (δ) are reported in ppm relative to TMS as an internal standard. *J* values are given in Hz. ^{13}C NMR spectra were recorded at 62.5 or 50 MHz. IR spectra were recorded with an FT-IR Perkin-Elmer instrument. MS was performed with MS 902S (AEI Kratos) spectrometer. TLC was carried out with 0.2 mm thick silica gel plates (GF_{254}). The columns were hand packed with silica gel 60 (200-300).

General procedure for the preparation of alkoxymethylene malonates (9a-d)

A mixture of activated methylene derivative (5 mmol), triethyl orthoformate (1-1.5 equiv.) and acetic anhydride (1-1.5 equiv.) was irradiated under microwave (CEM Discover System) at 125 °C for the appropriate time (see Table 1). After cooling, the crude products were purified by flash chromatography to afford the corresponding alkoxymethylenemalonates.

The yields of **9** and conversions of **7** were determined by capillary gas chromatography using an internal standard (Table 5). All these products have already been described in the literature.[16]

Table 5: GC conditions and retention times for reactants and products

Compd	GC column, temperature program	Internal standard	Retention times (min) Standard	**7**	**9**
9a	DB1 (30 m x 0.25 mm x 0.1 μm), injector and detector at 250 °C, 50 °C-250 °C with 10 °C min^{-1}, carrier gas helium 70 kPa	ethyl benzoate	8.27	3.64	9.61
9b	BP1 (12 m x 0.25 mm x 0.1 μm), injector and detector at 250 °C, 70 °C-250 °C with 10 °C min^{-1}, carrier gas helium 53 kPa	methyl benzoate	2.85	1.82	5.95, 6.20 (*Z*+*E*)
9c	DB1 (30 m x 0.25 mm x 0.1 μm), injector and detector at 250 °C, 80 °C-250 °C with 10 °C min^{-1}, carrier gas helium 70 kPa	ethyl benzoate	6.01	3.90	8.74
9d	BP1 (12 m x 0.25 mm x 0.1 μm), injector and detector at 250 °C, 70 °C-250 °C with 10 °C min^{-1}, carrier gas helium 53 kPa	methyl benzoate	2.85	1.21	3.89

3-(Ethoxymethylene)pentane-2,4-dione (9a) ^{1}H NMR ($CDCl_3$) δ 1.43 (t, *J* = 7.2 Hz, 3H), 2.34 (s, 3H), 2.41 (s, 3H), 4.28 (q, *J* = 7.4 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 29.0, 31.8, 66.9, 121.7, 165.7, 196.8, 197.5. IR (cm^{-1}): ν = 1676, 1622, 1582, 1135. MS (m/z) 156 (M^+).

2-Ethoxymethylene-3-oxobutanoic acid ethyl ester (9b): two isomers Z and E were observed. ^{1}H NMR ($CDCl_3$) δ 1.27-1.42 (m, 6H), 2.33 and 2.39 (s, 3H), 4.19-4.33 (m, 4H), 7.63 and 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.0, 28.5 and 31.4, 60.3 and 60.4, 72.5, 113.2 and 114.0, 163.9, 165.1, 195.0 and 196.5. IR (cm^{-1}): ν= 1726, 1702, 1630, 1135. MS (m/z) 186 (M^+).

2-Cyano-3-ethoxyacrylic acid ethyl ester (9c) ^{1}H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3H), 1.44 (t, *J* = 7.3 Hz, 3H), 4.22-4.39 (m, 4H), 8.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.0, 61.4, 73.7, 86.2, 112.6, 162.8, 172.2. IR (cm^{-1}): ν = 2227, 1713, 1619, 1130. MS (m/z) 169 (M^+).

2-(Ethoxymethylene)malononitrile (9d) ^{1}H NMR ($CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.5, 66.4, 109.3, 111.5, 173.7. IR (cm^{-1}): ν = 2228, 1612, 1008. MS (m/z) 122 (M^+).

General procedure for the preparation of aminomethylenemalonates (10a-e) from aniline.

A mixture of aniline (0.2 mL, 2.19 mmol) and alkoxymethylene compound (2.19 mmol) was submitted to microwave irradiation (Prolabo-Synthewave 402) at 70 °C for 2 min. The reaction mixture was cooled to rt and diluted with dichloromethane. After evaporation, the crude products were purified by flash chromatography (AcOEt : heptane = 2 : 8) to gave the corresponding aminoethylene malonates. All products have already been described in the literature.

3-(Phenylaminomethylene)pentane-2,4-dione (10a)[17] mp 85 °C (lit., 88°C). ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.57 (s, 3H), 7.17-7.27 (m, 3H), 7.39-7.42 (m, 2H), 8.25 (d, *J*=12.7 Hz, 1H), 12.74 (d, *J* = 12.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.4, 32.1, 113.3, 117.9, 125.8, 130.0, 139.1, 151.9, 194.9, 201.2. IR (cm^{-1}): ν = 3054, 2998, 1628, 1600. MS (m/z) 203 (M^+).

2-Acetyl-3-(phenylamino)acrylic acid ethyl ester (10b)[17,18] two isomers *Z* and *E* were observed (*E* : *Z* = 90 :10) mp 38-41 °C (lit., 41-43 °C). ^{1}H NMR ($CDCl_3$) δ 1.25-1.42 (m, 3H, *E* and *Z*), 2.48 (s, 3H, *Z*), 2.54 (s, 3H, *E*), 4.20-4.33 (m, 2H, *E* and *Z*), 7.13-7.20 (m, 3H), 7.33-7.41 (m, 2H), 8.49 (d, *J* = 13 Hz, 1H, *E*), 8.62 (d, *J* = 14 Hz, 1H, *Z*), 12.76 (d, *J* = 13 Hz, 1H, *E*); ^{13}C NMR ($CDCl_3$) δ 14.5, 31.2, 59.9, 102.6, 117.7, 125.5, 129.8, 139.0, 152.0, 166.9, 200.2. IR (cm^{-1}): ν = 2977, 1702, 1636, 1600, 1576. MS (m/z) 233 (M^+).

2-Cyano-3-(phenylamino)acrylic acid ethyl ester (10c)[6,19] two isomers *Z* and *E* were observed (*E* : *Z* = 75 :25) mp 114 °C (lit., 108 °C). ^{1}H NMR ($CDCl_3$) δ 1.31-1.41 (m, 3H, *E* and *Z*), 4,29 (q, 2H, *E* and *Z*), 7,08-7,27 (m, 3H), 7.37-7.45 (m, 2H), 7,88 (d, *J* = 14 Hz, 1H, *Z*), 8.16 (d, *J* = 15 Hz, 1H, *E*), 8.43 (d, *J* =

15 Hz, 1H, *E*), 10.74 (d, *J* = 14 Hz, 1H, *Z*); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.2, 66.7, 115.8, 117.1 (*Z*), 117.4 (*E*), 125.5 (*E*), 125.7 (*Z*), 129.9 (*E*), 130.0 (*Z*), 138.3 (*Z*), 138.8 (*E*), 152.0, 166.7. IR (cm^{-1}): ν = 2214, 1702, 1672, 1634, 1603, 1589. MS (m/z) 216 (M^+).

2-(Phenylaminomethylene)malononitrile (10d)[19] mp 245-247 °C (lit., 240-242 °C). ^{1}H NMR (DMSO-d_6) δ 7.13-7.45 (m, 5H), 8.50 (d, *J* = 14 Hz, 1H), 11.13 (d, *J* = 14 Hz, 1H) ; ^{13}C NMR (DMSO-d_6) δ 53.0, 115.3, 117.6, 119.0, 126.2, 130.4, 140.2, 156.6. IR (cm^{-1}): ν = 3211, 2223, 2210, 1659, 1593. MS (m/z) 169 (M^+).

2-(Phenylaminomethylene)malonic diethyl ester (10e)[6,12,13] mp 47-49 °C (lit., 49-51 °C). ^{1}H NMR ($CDCl_3$) δ 1.27-1.40 (m, 6H), 4.18-4.34 (m, 4H), 7.10-7.17 (m, 3H), 7.32-7.40 (m, 2H), 8.52 (d, *J*=14 Hz, 1H), 11.00 (d, *J* = 13 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.5, 60.2, 60.5, 93.5, 117.2, 125.0, 130.0, 139.3, 152.0, 165.8, 169.1. IR (cm^{-1}): ν = 3207, 3051, 2988, 1691, 1642, 1598. MS (m/z) 263 (M^+).

General procedure for the preparation of aminomethylenemalonates (11a-e) from 6-aminoquinoxaline

A mixture of 6-aminoquinoxaline (0.4 g, 2.76 mmol) and alkoxymethylene compound (2.76 mmol) was submitted to microwave irradiation (Prolabo-Synthewave 402) at 120 °C for 10 min. The reaction mixture was cooled to rt and diluted with dichloromethane. After evaporation, the crude products **(11a)** and **(11b)** were purified by flash chromatography (AcOEt : heptane = 6 : 4). In the case of the products **(11c)** and **(11d)**, they were isolated by filtration after washing with dichloromethane.

3-(Quinoxalin-6-ylaminomethylene)pentane-2,4-dione (11a) mp 158-161 °C. ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 2.60 (s, 3H), 7.62 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H), 7.85 (d, 1H), 8.15 (d, *J* = 9.3 Hz, 1H), 8.41 (d, *J* = 12.2 Hz), 8.82 (s, 1H), 8.86 (s, 1H), 12.92 (d, *J* = 11.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.4, 32.2, 113.9, 114.7, 122.3, 131.7**,** 140.3, 141.0, 143.8, 144.4, 146.1, 150.6, 195.0, 201.8. IR (cm^{-1}): ν = 1641. MS (m/z) 255 (M^+). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found C, 65.63; H, 5.00; N, 16.21.

2-Acetyl-3-(quinoxalin-6-ylamino)acrylic acid ethyl ester (**11b)** mp 116-117 °C. ^{1}H NMR ($CDCl_3$) δ (*E*-): 1.44 (t, *J* = 7.3 Hz, 3H), 2.55 (s, 3H), 4.33 (q, *J* = 7.3 Hz, 2H), 7.64 (dd, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.69 (d, *J* = 12.7 Hz, 1H), 8.82 (s, 1H), 8.87 (s, 1H), 12.97 (d, *J* = 12.2 Hz, 1H); (*Z*-): 1.44 (t, *J* = 7.3 Hz, 3H), 2.63 (s, 3H), 4.33 (q, *J* = 7.3 Hz, 2H), 7.64 (dd, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.69 (d, *J* = 12.7 Hz, 1H), 8.82 (s, 1H), 8.87 (s, 1H), 11.29 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 31.4, 60.3, 104.4, 114.2, 122.1, 131.5**,** 140.3, 140.9, 143.8, 144.3, 146.1, 150.9, 166.5, 200.9. IR (cm^{-1}): ν = 1712, 1644, 1624. MS (m/z) 285 (M^+). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found C, 62.91; H, 5.21; N, 14.35.

2-Cyano-3-(quinoxalin-6-ylamino)acrylic acid ethyl ester (11c) mp 207-208 °C. ^{1}H NMR (DMSO-d_6)

δ (*E*-): 1.28 (t, *J* = 7.3 Hz, 3H), 4.25 (m, 2H), 8.08 (m, 3H), 8.55 (s, 1H), 8.74 (d, *J* = 13.2 Hz, 1H), 8.86 (s, 1H), 8.92 (s, 1H), 11.14 (s, 1H); (*Z*-): 1.28 (t, *J* = 7.3 Hz, 3H), 4.25 (m, 2H), 8.08 (m, 3H), 8.74 (d, *J* = 13.2 Hz, 1H), 8.86 (s, 1H), 8.92 (s, 1H), 10.98 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (*E*-): 14.3, 60.7, 76.7, 114.7, 115.6, 122.3, 130.5**,** 139.8; 140.9, 142.9, 144.6, 146.4, 152.4, 164.3; (*Z*-): 14.3, 61.6, 75.6, 114.7, 115.6, 122.5, 130.5**,** 139.8; 140.9, 142.9, 144.6, 146.4, 153.6, 165.9. IR (cm^{-1}): ν = 2213, 1716, 1679, 1633, 1620. MS (m/z) 268 (M^+). Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found C, 62.15; H, 4.32; N, 20.55.

2-(Quinoxalin-6-ylaminomethylene)malononitrile (11d) mp 270 °C. ^{1}H NMR (DMSO-d_6) δ 8.04 (m, 3H), 8.84 (m, 3H), 8.86 (s, 1H), 8.92 (s, 1H), 11.45 (d, *J* = 12.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 53.9, 113.7, 114.8; 115.9, 122.0, 130.3**,** 139.8, 140.2, 142.7, 144.7, 146.4, 156.0. IR (cm^{-1}): ν = 3293, 3210, 3020, 2220, 1646. MS (m/z) 221 (M^+). Anal. Calcd for $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found C, 64.92; H, 3.15; N, 31.93.

2-(Quinoxalin-6-ylaminomethylene)malonic acid diethyl ester (11e) mp 112-115 °C. ^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.42 (t, *J* = 7.0 Hz, 3H), 4.29 (m, 2H), 4.36 (m, 2H), 7.58 (dd, *J* = 2.4 Hz, *J* = 9.3 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.69 (d, *J* = 13.2 Hz, 1H), 8.79 (s, 1H), 8.83 (s, 1H), 11.28 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.5, 60.5, 60.9, 96.1, 113.2, 121.9, 131.5, 140.5, 140.7, 144.0, 146.1, 150.8, 165.2, 168.9. IR (cm^{-1}): ν = 1693, 1694, 1615. MS (m/z) 315 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.95; H, 5.43; N, 13.33. Found C, 60.25; H, 5.25; N, 13.05.

General procedure for the classical preparation of quinolones (12b, c, e)

Aminoethylene compound **(10b, c, e)** (500 mg) and diphenyl ether (10 g) were heated in metallic bath at the temperature and for the time as reported in Table 3. The reaction mixture was quenched and rapidly brought to 80 °C and 50 mL of heptane was added. The solid precipitating upon cooling was collected by filtration and washed several times with heptane. All products have already been described in the literature.

General procedure for the solvent-free preparation of quinolone (12e)

2-Phenylaminomethylenemalonic acid diethyl ester **(10e)** (500 mg, 1.9 mmol) was heated using metallic bath at 380 °C, with mechanical stirring, for the appropriate time as reported in Table 4. The reaction mixture was immediately cooled to rt and the cyclic product **(12e)** was precipitated with 10 mL of dichloromethane and was filtered off. The conversion of **(10e)** was determined by capillary gas chromatography CPSil 19 CB (30 m x 0.25 mm x 0.2 μm, with injector at 220 °C and detector at 250 °C, programming = 150 °C - 220 °C with 10 °C. min^{-1}) using an internal standard (diphenylphthalate).

3-Acetylquinolin-4(1*H*)-one (12b)[20] mp 246 °C (lit., 240-244 °C). ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H), 7.38-7.73 (m, 3H), 8.21 (d, *J* = 8 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.8, 117.4, 118.6, 124.6,

125.4, 127.5, 132.2, 138.7, 143.8, 174.9, 196.1. IR (cm^{-1}): ν = 3427, 1671, 1622, 1568, 1539. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found C, 69.96; H, 4.77; N, 7.04.

1,4-Dihydro-4-oxoquinoline-3-carbonitrile (12c)[6,21] mp 300 °C (lit., 301 °C). ^{1}H NMR (DMSO-d_6) δ 7.49 (t, *J* = 7 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* =7 Hz, 1H), 8.13 (d, J = 7 Hz, 1H), 8.75 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 93.3, 116.5, 118.9, 124.7, 125.3, 133.0, 138.8, 146.4, 174.2. IR (cm^{-1}): ν = 2224, 1629, 1557, 1536. Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.44. Found C, 69.61; H, 3.45; N, 16.81.

1,4-Dihydro-oxoquinoline-3-carboxylic acid ethyl ester (12e)[13,22] mp 272-274 °C (lit., 269-270 °C). ^{1}H NMR (DMSO-d_6) δ 1.31 (t, *J* = 7 Hz, 3H), 4.25 (q, *J* = 7 Hz, 2H), 7.60 (m, 3H), 7.82 (d, *J* = 8 Hz, 1H), 8.60 (s, 1H), 12.38 (s, 1H). IR (cm^{-1}): ν = 3162, 3128, 1697, 1622. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found C, 66.33; H, 5.33; N, 6.25.

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