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Convenient Gould-Jacobs Synthesis of 4-Quinolone Core Using Eaton's Reagent †

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Abstract

The Gould-Jacobs reaction for the synthesis of ethyl 4-quinolone-3-carboxylate derivatives is described. Thus, the condensation of 4-subtituted anilines and EMME to give the corresponding diethyl anilinomethylene malonate was carried out via neat MW irradiation or refluxing ethanol. These intermediates underwent the Eaton's reagent catalyzed cyclisation in good to excellent yields. For the first step, the MW reaction took only 7 min compared to the two hours required for the conventional heating, yet the yields were comparable in almost all cases. A series of eight 4-quinolone derivatives was obtained in good yields under mild conditions and short reaction times.

Keywords: synthesis; 4-quinolones; Eaton's reagent

1. Introduction

Naturally occurring or synthetic heterocycles with a quinoline nucleus represent an important source of bioactive compounds. Meanwhile, 4-quinolone and 2-quinolone, which are the tautomers of 4-hydroxyquinoline and 2-hydroxyquinoline, respectively, represent the core of several broad-spectrum synthetic antibiotics [1].

Our research group has developed a series of 4-phenyl-3-amino-2-quinolone derivatives, which exhibited activity against *Plasmodium falciparum*, the parasite that causes malaria, while others were found to inhibit angiogenesis [2]. Later, a series of polycyclic 4-quinolones was synthesized via MW irradiation using a one-pot reaction from anthranilic acid and cyclanones [3]. Furthermore, the selective synthesis of 4-methyl-2-quinolone was described, employing the Eaton's reagent and avoiding the use of mineral acids and expensive metal catalysts such as those described in the literature [4]. Eaton's reagent, which consists in 7.7% phosphorus pentoxide dissolved in methanesulfonic acid, is easily available and has advantages such as controlled reaction conditions and low environmental impact [5]. Although it has a strongly acidic character due to its composition, it is a good solvent because it is an organic acid and has a lower density than mineral acids.

A recent review describes a wide variety of chemical methods leading to quinoline-4-ones [6] and one of the most prominent is the Gould–Jacobs reaction [7]. It involves the condensation of aniline **1** and diethyl ethoxymethylidenedimalonate (EMME) **2** to give the intermediate diethyl anilinomethylene malonate **3**, which is cyclized upon further

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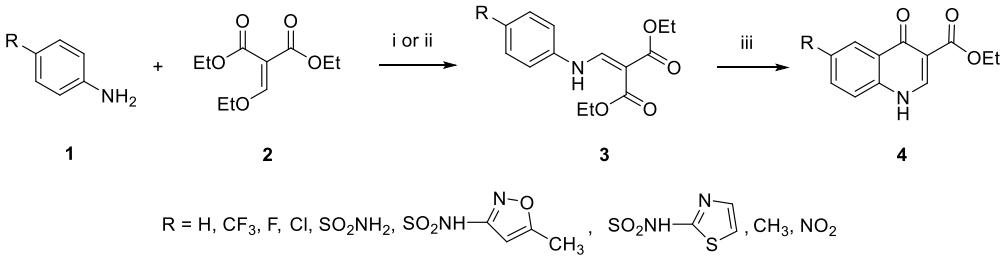
heating, usually under drastic conditions, to give ethyl 4-quinolone-3-carboxylate **4** (Scheme 1). In this work, we describe and improved Gould-Jacobs reaction promoted by MW in the first step and employing the Eaton's reagent for the thermal cyclization to afford a series of 6-substituted quinoline-4-ones of pharmaceutical interest.

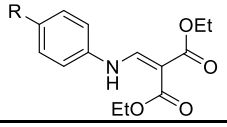


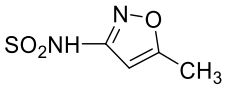
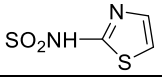
Scheme 1. Gould-Jacobs synthesis of ethyl 4-quinolone-3-carboxylates **4**. Reagents and conditions in this work: (i) neat, MW, 7 min or (ii) EtOH, reflux, 2 h; (iii) Eaton's reagent, 80–100 °C, 2 h.

2. Results and Discussion

The neat reaction of aniline and EMME to prepare the anilinomethylene malonate **3** has been reported and in most cases, it required between 100 or 120 °C and a reaction time of 4 h [8,9]. Other authors employed ethanol at refluxing temperature [10] and even at room temperature [11]. For this stage, we have carried out two procedures. Thus, an equimolar neat mixture of 4-subtituted anilines and EMME was subjected to MW irradiation and the corresponding intermediate product **3** was achieved in 7 min. On the other hand, the same reaction was developed under refluxing ethanol for 2 h, to compare their performance (Scheme 1). Although the yields were higher in EtOH or similar in some cases, MW irradiation shortened the reaction times (Table 1). The intermediate products **3** were crystallized from the proper solvent and the spectroscopical data and melting point values of **3a**–**3e** and **3g**–**3i** agreed the literature, whereas **3f** was a novel structure.

Table 1. Comparative yields for the synthesis of anilinomethylene malonates **3a**–**3i** and their melting points values [1].



Entry	Compd.	R	% Yield MW	% Yield EtOH	m.p. °C [2]
1	**3a**	H	50	60	43–45
2	**3b**	CF_3	40	62	88–89
3	**3c**	F	15	25	66–68
4	**3d**	Cl	15	74	76–80
5	**3e**	SO_2NH_2	40	75	148–150
6	**3f**		81	60	166–168
7	**3g**		d [3]	77	168–169
8	**3h**	CH_3	75	80	43–45
9	**3i**	NO_2	80	63	130–132

[1] Purified products; [2] physical data according to literature, except the novel 3f; [3] decomposes after 5 min.

For the cyclization step to the quinoline-4-one **4**, high reaction temperatures were required when diphenyl ether was the solvent [8,9] as well as harsh conditions, such as PPA/$POCl_3$ at 75 °C for 12 h [10], Dowtherm or flash vacuum pyrolysis (FVP) [12]. The commercially available Eaton's reagent (1:10 *w*/*w* P_2O_5 in methanesulfonic acid) was found to be an ideal alternative, requiring milder conditions, and resulting in quantitative yields. Only one author reported both, the use of the Eaton's reagent and diphenyl ether to prepare in good yields the sole compound **4a** [9].

Therefore, the intermediate products **3a**–**3i** reacted with Eaton's reagent at 100 °C for 2 h. An average yield of 60% was obtained for the quinoline-4-ones **4a**–**4h**, which were further crystallized from EtOH, and their physical data analyzed and compared with the literature. Derivative **4i**, possessing a 4-nitro substituent, could not be isolated. The dark-colored solid obtained after isolation consisted of a mixture of products that were difficult to purify. In conclusion, it was possible to extend the use of Eaton's reagent in the Gould-Jacobs reaction to prepare structures with a 4-quinolone skeleton, which also represent starting materials in the search for new antimicrobial agents.

3. Materials and Methods

Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Bruker 600 spectrometer. The operating frequencies for protons and carbons were 600 and 151 MHz, respectively. The chemical shifts (δ) were given in ppm. IR spectra were recorded on an FT Thermo Scientific from KBr discs. Analytical TLCs were performed on DC-Alufolien Kieselgel 60 F 254 Merck. Microwave-assisted reactions were carried out in a Glass vial G10, Anton Paar Monowave 400 (Serial Number: 81920884, Instrument Software Version: 4.10.9376.7).

3.1. General Procedure for the Synthesis of Diethyl Anilinomethylene Malonate **3a–3i**

Method i: A neat mixture of 2 mmol of 4-substituted aniline and 2 mmol of EMME was subjected to MW irradiation at 170 °C and 850 W for 7 min. The mixture was cooled to room temperature to give a solid product, which was then crystallized from the appropriate solvent. Method ii: A mixture of 3 mmol of 4-substituted aniline and 3 mmol of EMME was refluxed in 10 mL anhydrous EtOH for 2 h. The mixture was cooled to room temperature to give a solid product, excepting for **3a** and **3h**, where the EtOH was evaporated before. The spectral characteristics of compounds **3a**–**3e** and **3g**–**3i** are identical to the reported data. Yields and m.p. values are depicted in Table 1.

Diethyl 2-(((4-(N-(5-Methylisoxazol-3-yl)sulfamoyl)phenyl)amino)methylene)malonate **3f**

White powder, 81% yield (method i). ^1H NMR (DMSO-d_6) δ (ppm): 11.41 (s, 1H, SO_2NH), 10.70 (d, *J* = 13.5 Hz, 1H, NH), 8.39 (d, *J* = 13.5 Hz, 1H, =CH), 7.84 (d, 2H, arom.), 7.58 (d, 2H, arom.), 6.15 (s, 1H, het.), 4.22 (m, 2H, CH_2), 4.13 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.25 (t, 6H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 170.82, 167.24, 165.20, 157.97, 150.02, 143.99, 134.65, 129.06, 118.08, 96.42, 95.87, 60.45, 60.25, 14.68, 14.59, 12.52. IR ν (cm^{-1}): 1671.3, 1637.9, 1589.2, 1250.7, 1165.6, 829.06 (Figures S1–S3).

3.2. General Procedure for the Synthesis of Ethyl 4-Quinolone-3-Carboxylates **4a–3h**

A mixture of 2 mmol of derivative 3 and 2 mL of Eaton's reagent was heated at 100 °C for 2 h. The reaction mixture was cooled to rt and then poured into a saturated $NaHCO_3$ solution. The product was filtered off, washed, and then crystallized from EtOH.

3.2.1. Ethyl 4-oxo-1,4-Dihydroquinoline-3-Carboxylate **4a**

Pale yellow powder, 65% yield, m.p. 271–274 °C (Lit. 271–273 °C)[9]

3.2.2. Ethyl 4-oxo-6-(Trifluoromethyl)-1,4-Dihydroquinoline-3-Carboxylate **4b**

Pale brown powder, 75% yield, m.p. 288–287 °C (Lit. 290–292 °C)[10]

3.2.3. Ethyl 6-Fluoro-4-oxo-1,4-Dihydroquinoline-3-Carboxylate **4c**

Pale brown powder, 40% yield, m.p. 280–285 °C (Lit. 288–290 °C)[10]

3.2.4. Ethyl 6-Chloro-4-oxo-1,4-Dihydroquinoline-3-Carboxylate **4d**

Light beige powder, 40% yield, m.p. 295–298 °C (Lit. 295–296 °C)[13]

3.2.5. Ethyl 4-oxo-6-Sulfamoyl-1,4-Dihydroquinoline-3-Carboxylate **4e**

Beige powder, 80% yield, m.p. > 290 °C

3.2.6. Ethyl 6-(N-(5-Methylisoxazol-3-yl)sulfamoyl)-4-oxo-1,4-Dihydroquinoline-3-Carboxylate **4f**

Beige powder, 62% yield, m.p. > 290 °C

3.2.7. Ethyl 4-oxo-6-(N-(Thiazol-2-yl)sulfamoyl)-1,4-Dihydroquinoline-3-Carboxylate **4g**

Beige powder, 72% yield, m.p. > 290 °C

3.2.8. Ethyl 6-Methyl-4-oxo-1,4-Dihydroquinoline-3-Carboxylate **4h**

Beige powder, 15% yield, m.p. > 290 °C (Lit. > 280 °C)[14]

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Figures S1–S3: ^{1}H and ^{13}C NMR and IR spectra of **3f**.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

DMSO	dimethyl sulfoxide
EMME	diethyl ethoxymethylenemalonate
FVP	flash vacuum pyrolysis
MW	microwave
PPA	polyphosphoric acid

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