ECSOC-29
2025
Conference

The 29th Intl Electronic Conference on Synthetic Organic Chemistry

14–28 November 2025 | Online

MDPI

Convenient Gould-Jacobs synthesis of 4-quinolone core using Eaton's reagent

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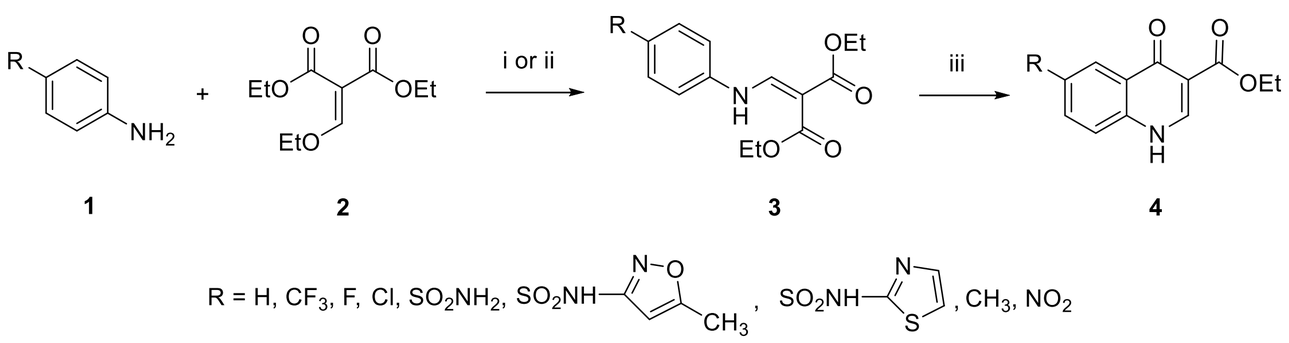
INTRODUCTION & AIM

Naturally occurring or synthetic heterocycles with a quinoline nucleus represent an important source of bioactive compounds. Our research group has described the selective synthesis of 4-methyl-2-quinolone[1] employing the Eaton´s reagent, which consists in 7.7 % phosphorus pentoxide dissolved in methanesulfonic acid and has advantages such as controlled reaction conditions and low environmental impact[2]. The Gould–Jacobs reaction involves the condensation of aniline **1** and diethyl ethoxymethylidene dimalonate (EMME) **2** to give the intermediate diethyl anilinomethylene malonate **3**, which is cyclized upon further heating, usually under drastic conditions, to give ethyl 4-quinolone-3-carboxylate **4** (Scheme 1)[3,4]. 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.

METHOD

Scheme 1. Gould-Jacobs synthesis of ethyl 4-quinolone-3-carboxylates **4**[1]



[1]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.

Synthesis of diethyl anilinomethylene malonate **3a-3i**

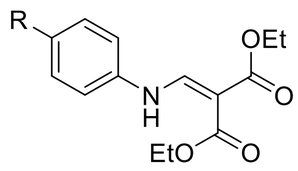
Method i: A neat mixture of 2 mmol of 4-substituted aniline and 2 mmol of EMME was subjected to MW irradiation at 170 ºC and 850 W for 7 min. The mixture was cooled to room temperature to give a solid product, which was then crystallized from the appropriate solvent. Method ii: A mixture of 3 mmol of 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. 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.

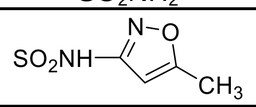
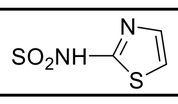
Synthesis of ethyl 4-quinolone-3-carboxylates **4a-3h**

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.

RESULTS & DISCUSSION

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 as well as harsh conditions, such as PPA/$POCl_3$ at 75 °C for 12 hours, Dowtherm or flash vacuum pyrolysis (FVP). Therefore, the intermediate products **3a-3i** reacted with Eaton´s reagent at 100 °C for 2 hours. 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.

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 valuable starting materials in the search for new antimicrobial agents.

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