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Rapid synthesis of 2,3-disubstituted-quinazolin-4-ones enhanced by microwave-assisted decomposition of formamide

Ioannis K. Kostakis,[a] Abdelhakim Elomri,[a] Elisabeth Seguin,[a] Mauro Iannelli[b] and Thierry Besson[a,*]

[a]*UMR CNRS 6014, Groupe de Chimie Pharmaceutique, Université de Rouen, UFR Médecine-Pharmacie, 22 Boulevard Gambetta, F-76183 Rouen Cedex, France*
[b]*Milestone S.r.l., Via Fatebenefratelli, 1/5, 24010 Sorisole (BG), Italy*

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Abstract—An efficient methodology for the preparation of a series of 2,3-disubstituted-quinazolin-4(3*H*)-ones is described via a three step reaction from anthranilic acid. The obtained results also reveal that microwave-assisted rapid decomposition of formamide under controlled conditions of power, temperature and time is a very convenient source of ammonia for the synthesis of 2-substituted-quinazolin-4(3*H*)-ones and other rings.

The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids[1] such as glycosminine,[2] echinozolinone,[3] deoxyvasicinone,[4] rutaecarpine[5] and drugs like methaqualone[6] (Fig. 1). The natural quinazolinones and their synthetic analogous, possess a variety of biological activities, including antimalarial,[7] anticonvulsant,[8] antibacterial,[9] antidiabetic[10] and anticancer.[11] Thus, due to the diverse range of the pharmacological activities of quinazolinones and their derivatives, there are numerous methods available for their synthesis.[12] Among them, the main synthetic routes employ 2-aminobenzoic acid, 2-aminobenzamide, isatoic anhydride, *N*-arylnitrilium salts and 3,1-benzoxazinones as appropriate precursors.

In previous works we have synthesized a series of novel heterocycles where the quinazolinone ring was fused with a thiazole, indole or benzimidazole core.[13] Continuing our studies on this class of compounds, we considered to prepare 2,3-disubstituted-quinazolin-4(3*H*)-one derivatives that can be employed as intermediates in the synthesis of functional bioactive molecules.

In these compounds, an alkyl group was inserted into the quinazolinone ring in position 2 with the aim to elucidate the structural requirements and thus contribute to structure–activity studies.

The advantages of using microwave dielectric heating for performing organic reactions are well known[14] (e.g., remarkable reduction of reaction time, improved yields and cleaner reactions than the ones performed under conventional thermal heating). Therefore, we wish to report here the microwave-assisted synthesis of substituted quinazolin-4-ones via activation and decomposition of formamide. The experiments were performed under pressurized conditions using the novel 'hybrid' microwave platform MultiSYNTH® (Milestone S.r.l., Italy).[15] The reported microwave conditions were optimized varying applied power and temperature.

The synthesis of the desired quinazolin-4(3*H*)-ones **6a**–**e** and **7a**–**e** was performed in three steps starting from anthranilic acid (**1**) and using 3,1-benzoxazinones **2** and **3** as intermediates (Scheme 1). This approach was inspired by the previous works of Dabiri et al.[12d] and Liu et al.[12h] who described 2,3-disubstituted-quinazolines prepared under microwaves via similar intermediates. Our work exploits the dielectric properties of the molecules and their capacity to react specifically under the microwaves in order to reduce the number of reactants involved and then to develop eco-compatible methods.

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* Corresponding author. Tel.: +33 (0)235148399; fax: +33 (0)235148423; e-mail: thierry.besson@univ-rouen.fr

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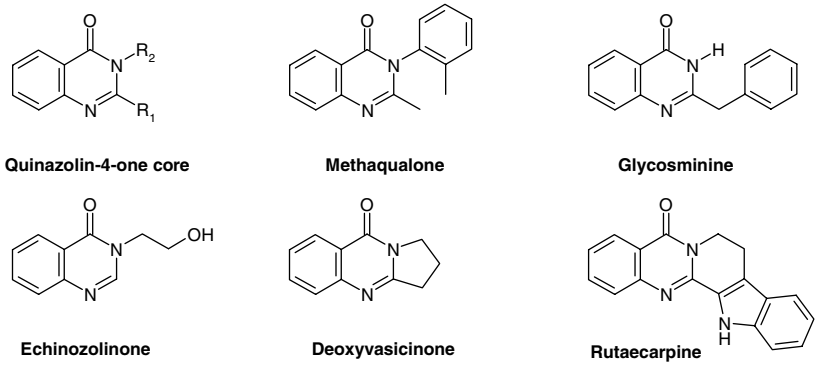
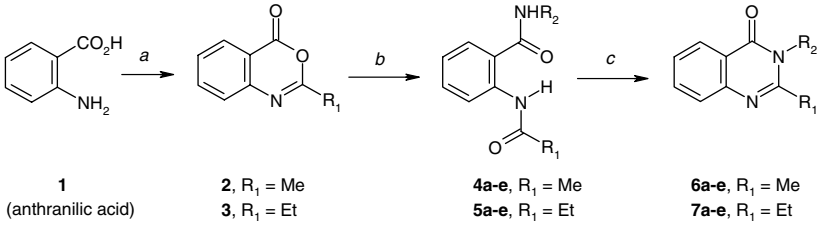


Figure 1. Structure of the quinazoline core and various natural and synthetic alkaloids.



Scheme 1. Reagents and conditions: (a) (R_1 = Me): acetic anhydride, MW (200 W), 130 °C, 10 min; (R_1 = Et): propionic anhydride, MW (200 W), 160 °C, 10 min; (b) aliphatic amine (R_2–NH_2) (2 equiv), CH_2Cl_2, rt, 10–40 min; (c) formamide, MW (200 W), 170 °C, 10 min.

The first synthetic step involved the condensation of anthranilic acid (**1**) with acetic or propionic anhydride to afford the desired benzoxazinones (**2** and **3**, respectively) in quantitative yields. After evaporation of the excess of anhydride under reduced pressure, the crude product was used without any further purification. In fact, the methyl analogue is very moisture sensitive and could be easily hydrolyzed into the *N*-acylanthranilic acid.[16]

Intermediates **2** and **3** were then totally converted into **4a**–**e** and **5a**–**e** through treatment with an excess of the appropriate aliphatic amine. Finally, the obtained diamides were subjected to microwave-assisted cyclocondensation to give the desired quinazolinones **6a**–**e** and **7a**–**e** in good yields (Table 1).

According to the literature, this final step usually involves long heating (several hours) of the diamide intermediates in various solvents such as acetic acid, xylene or dimethylformamide (DMF).[17] In preliminary experiments with many different solvents (e.g., acetic acid, *N*-methylpyrrolidone (NMP), methanesulfonic acid, acetic anhydride, xylene and formamide), we observed that the most favourable one was formamide. The complete conversion to quinazolin-4(3*H*)-ones using acetic acid and acetic anhydride was achieved only with prolonged reaction times (50 min or more). Performing the reaction in NMP afforded the desired product in low yields (at temperatures above 190 °C, the reaction yielded complicated mixtures of carbonaceous compounds and impurities), while the use of xylene was inconvenient due to its weak microwave absorbing character.

Although, methanesulfonic acid afforded good results, especially with the methyl analogues (striking reduction in reaction time), the isolation of the products in pure form was very difficult due to the large presence of decomposition products probably due to the highly attained temperature (200 °C).

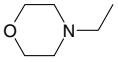
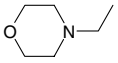
The use of formamide as the reaction solvent gave the most satisfactory results. The best results were obtained using a programmed irradiation at 200 W and a fixed temperature of 170 °C. Complete conversion was achieved within 10 min in good yields (see Table 1 for overall yields from anthranilic acid). As comparison, diamide **4a** was also subjected to the same reaction conditions (170 °C and formamide as solvent) under conventional thermal heating in a preheated oil bath. After a reaction time of 110 min, the overall yield of the cyclized product (**6a**) dropped to 76% (compared to 84% after 10 min under microwave irradiation, see Table 1).

Through optimization runs it was possible to observe that working at a temperature of 200 °C, the desired quinazolinones **6a**–**e** and **7a**–**e** were formed as the major products accompanied by minor amounts of the non-alkylated quinazolin-4(3*H*)-ones (**8** and **9**, respectively, see Scheme 2).

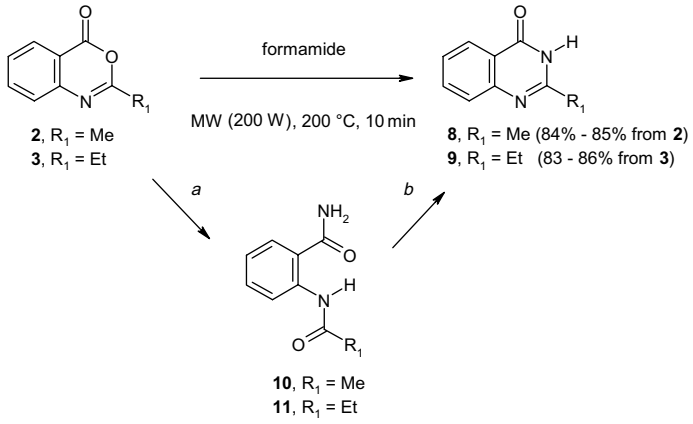
The thermal decomposition of formamide was already described in the literature[18] and there are a few examples where it was not used only as a solvent.[19,20] According to these results, we can suggest that formamide could be, under the applied reaction conditions, the source of the ammonia that generates the unexpected mono-2-substituted-4(3*H*)-quinazolinones **8** and **9**.

This simple procedure for the synthesis of the monosubstituted quinazolinones would obviously be of great

Table 1. Synthesis of 3*H*-quinazolin-4-ones from anthranilic acid

Starting compound	R_2NH_2 (equiv)	Product	R_1	R_2	Yield[a] (%)
2	2	**6a**	Me	Me	84
2	2	**6b**	Me	*n*-Bu	75
2	2	**6c**	Me		77
2	2	**6d**	Me		83
2	2	**6e**	Me		77
3	2	**7a**	Et	Me	87
3	2	**7b**	Et	*n*-Bu	74
3	2	**7c**	Et		85
3	2	**7d**	Et		86
3	2	**7e**	Et		87

[a] Overall yield from anthranilic acid.



Scheme 2. Reagents and conditions: (a) NH_3 20% aq (8 equiv), THF, rt; 10–20 min; (b) NaOH 5% aq, MW (100 W), 90 °C, 4 min.

interest for synthetic chemists. In fact, formamide could be a cheap and easy to handle ammonia source for the introduction of N-3 in the quinazolinone ring. To the best of our knowledge, there are no reports on the use of formamide as an ammonia synthon for the synthesis of heterocyclic compounds under microwave irradiation.

According to the previous observations, 10 min of irradiation at 200 W (200 °C) of a mixture of 3,1-benzoxazinones (**2** or **3**) and formamide, afforded the expected mono-2-substituted-4(3*H*)-quinazolinones **8** and **9** in very good yields (84% and 83%, respectively) (Scheme 2).

With the aim to confirm our results, we reinvestigated, using microwave irradiation, the traditional conditions described in the literature for the synthesis of 2-substituted-4(3*H*)-quinazolinones via treatment of the appropriate 3,1-benzoxazinones with aqueous ammonia (8 equiv).[21] By analogy to the above mentioned procedure for the disubstituted quinazolinones, the benzoxazinones (**2** and **3**) were first converted to the corresponding acylanthranilamides. The reaction took place at room temperature in 20% aqueous ammonia solution to afford products **10** and **11** (Scheme 2). The microwave-assisted cyclocondensation with a preset power of 100 W and a fixed temperature of 90 °C allowed ring closure of the intermediate diamides **10** and **11** and provided the target mono-2-substituted-quinazolin-4(3*H*)-ones **8** and **9** in 85% and 86% yields, respectively (Scheme 2). The overall yields of the two methods are comparable, nevertheless, the procedure with formamide as an ammonia source, is simpler and more convenient, and requires only two synthetic steps from anthranilic acid.

In conclusion, we have developed an efficient and novel methodology for the preparation of a series of 2,3-disubstituted-quinazolin-4(3*H*)-ones via a three step reaction from anthranilic acid and 3,1-benzoxazinones as inter-

mediates, with formamide as the solvent. Considering that the synthesis of these molecules is a well established procedure by conventional methods,[22] the proposed synthetic strategy could be a general method for the synthesis of 2,3-dialkyl-quinazolin-4(3*H*)-ones.

As we have previously shown in our study of the microwave-assisted decomposition of DMSO, and its use in Pictet–Spengler heterocyclization,[23] reactants may have different behaviours under microwaves, depending on the power input, the temperature reached, and also, on the pressure obtained in the vials. Then, we have demonstrated here that microwave-assisted rapid decomposition of formamide can be controlled under well established conditions of power, temperature and time. This phenomenon is a very convenient source of ammonia for the synthesis of mono-2-substituted-quinazolin-4(3*H*)-ones. Because it may also avoid the use of expensive or difficult to handle reagents, it can be simply and efficiently extended to the synthesis of various heterocyclic derivatives.

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15. The 'hybrid' microwave platform MultiSYNTH® (Milestone S.r.l.), is a novel dedicated microwave system for synthetic applications. It allows a fast reaction optimization providing high energy density in a single-mode like configuration and an efficient scale-up (maximum working volume 300 ml) through parallel synthesis in a multi-mode configuration. The instrument features a special shaking system that ensures high homogeneity of the reaction mixtures. It is equipped with an indirect pressure-control through pre-calibrated springs at the bottom of the vessels shields and with both, contact-less infrared pyrometer (IRT) and fibre-optic contact thermometer (FO) for accurate temperature measurement. It is noteworthy that the IRT can be calibrated directly on the temperature read by the FO to ensure the highest accuracy and reproducibility. A complete description of this system is available at www.milestonesrl.com.
All the reactions were performed in sealed 10 ml vials. The software algorithm regulates the microwave output power according to the temperature. The temperature was controlled by FO and maintained constant for the desired reaction/irradiation time, after a ramp time of 1 min. At the end of the irradiation period, the reaction vessel was rapidly cooled to ambient temperature with compressed-air using the equipped cooling feature (gas-jet cooling). The minimal reaction times were determined by performing sequential series of identical reactions at constant temperature with different irradiation times. The completion of the reaction was estimated by TLC after each individual reaction period.
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