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Decomposition of formamide assisted by microwaves, a tool for synthesis of nitrogen-containing heterocycles

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ABSTRACT

Generation of ammonia via thermal decomposition of formamide was studied under microwave conditions to provide an efficient tool for the synthesis of nitrogen-containing heterocycles. Quinazolin-4-ones, which are known as building blocks for molecules with pharmaceutical interest, were chosen as examples. Our work confirms that reactants may have different behaviours under microwaves, depending on power input, reached temperature and pressure in the vials. Full control and fine tuning of these parameters are achievable using modern microwave technology.

In a near future, the use of adapted reactants and techniques offering operational, economic and environmental benefits, over conventional methods, will be crucial in the preparation and development of molecules with biological activity. Recently, the use of clean and more efficient technologies, like microwaves, has become a major stimulus for both industry and academia.[1,2] Recently developed commercial microwave systems[3] specific for synthesis offer improved opportunities for reproducibility, rapid synthesis, rapid reaction optimization and potential discovery of new chemistries. Among our recent projects, we decided to study the microwave stability of various solvents and products in order to detect the possible modifications of these reactants under microwaves, and then to study the possibility to perform novel chemical reactions. This strategy is inspired by earlier works described in the literature[4] and our experience on the microwave-assisted synthesis of heterocyclic molecules with pharmaceutical interest.[5] We recently explored efficient methodologies for the preparation of 2,3-disubstituted quinazolin-4(3*H*)-ones as building blocks for the synthesis of derivatives of numerous bioactive molecules[6] (e.g., gefitinib—Iressa®, vandetanib—Zactima®, erlotinib—Tarceva® and laptinib—Tyber®). In our study, formamide gave the most satisfactory results as reaction medium. Nevertheless, through optimization runs, some results revealed that microwave-assisted rapid decomposition of formamide under specific reaction conditions can be a source of ammonia that generates unexpected products.[7] The thermal decomposition of formamide was already described in the literature[8] and recently it has been exploited as both a surrogate for ammonia and a source of carbon monoxide in the same reaction.[9] With the aim to confirm and extend our previous results, we have investigated the possibility to control the rapid decomposition of formamide under well-established conditions of microwave power, temperature and time. Our first idea was to follow by gas-chromatography the degradation of formamide but, after some trials, we decided to come back on the synthesis of substituted-quinazolin-4(3*H*)-ones and use it as a model. To the best of our knowledge, this is the first example where this reactant has been used as a sole ammonia synthon for introduction of a nitrogen atom into heterocyclic rings under microwave irradiation. The microwave experiments reported in this note were performed under pressurized conditions using the novel 'hybrid' microwave platform MultiSYNTH® (Milestone S.r.l, Italy).[10] Reaction conditions were optimized varying applied power and temperature (measured by both fibre-optic contact thermometer and infrared pyrometer).

Due to the broad range of pharmacological activities of quinazolinones and their derivatives, there are numerous methods available for their synthesis.[11] Inspired by the previous works of Dabiri[11d] and Liu,[11h] our synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (**4**) was performed in three steps starting from anthranilic acid (**1**) and using 3,1-benzoxazinones (**2**) as intermediates (Scheme 1).[7] In these compounds, an alkyl group was inserted

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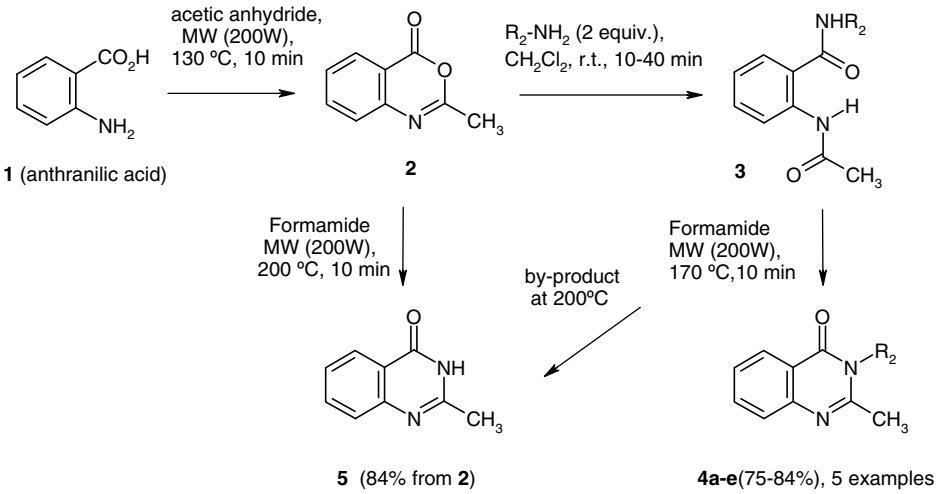


Scheme 1. Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones (**4a–e**) in three steps from anthranilic acid.[7]

into the quinazolinone ring in position 2 by nucleophilic attack of an appropriate aliphatic amine and a microwave-assisted cyclocondensation of the intermediate diamides (**3**).

We decided to focus our efforts on the last step of this synthesis. 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. This finding can be explained as a result of the high loss tangent of formamide ($\tan\delta = 0.56$) that guarantees a very efficient coupling with microwaves.[12] The best results were obtained using a programmed irradiation at 200 W and a fixed temperature of 170 °C (obtained with a ramp of 2 min). Complete conversion was achieved within 10 min in good yields (75–84%, 5 examples). Working at a temperature of 200 °C gave various amounts of unexpected mono-2-substituted-4(3*H*)-quinazolinones. The presence of such compounds could be rationalized through decomposition of formamide that generates ammonia and then the unexpected mono-alkylated products. According to the previous observations, 10 min of irradiation at 200 W (200 °C) of a mixture of 3,1-benzoxazinones (**2**) and formamide afforded the expected mono-2-substituted-4(3*H*)-quinazolinones in good yields (Scheme 1). The same reaction (stoichiometry and work up) was performed at various reaction times (1–4, 6 and 10 min), temperatures (100, 150, 170 and 200 °C) and irradiation power (200, 300 and 400 W). The results show that degradation of formamide is function of the final temperature but not of the power input. Nevertheless, a temperature close to 170 °C has to be reached to observe the degradation. Testing a traditional heating mode (sealed tube, pre-heated oil bath at 190–200 °C), we observed that generation of ammonia from formamide is also reaction time depending: heating the sealed tubes at 200 °C for 10 min, 1, 3 or 5 h showed that the first traces of the expected product are obtained after 3h and that complete conversion can be obtained in 5 h. Starting from various intermediate 3,1-benzoxazin-4-ones (with Et, Pr or Bn instead of Me in **2**), we also observed that different yields were obtained. Our first hypothesis was to consider that conventional thermal degradation of formamide was difficult to control and can induce modifications of the yields. In fact, after investigation, we noticed that the 3,1-benzoxazin-4-ones used were very moisture sensitive and could be easily hydrolyzed into the corresponding *N*-acylanthranilic acid.[13]

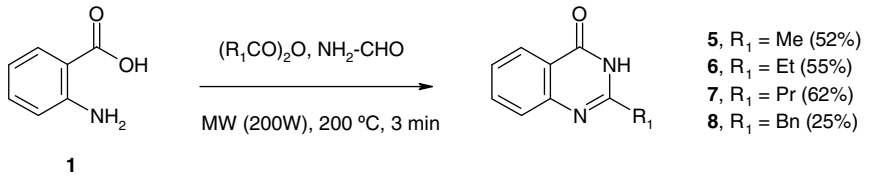
Considering the apparent kinetics of the two steps of the synthesis of product **5,** we planned a three-component procedure, where anthranilic acid, acetic anhydride and formamide were heated in sealed tubes at 200 °C (200 W) for 10 min.[10] Our hypothesis suggested that decomposition of formamide occurs rapidly during reaction of anthranilic acid and anhydride, and the in situ generated ammonia reacts with compound **2** as soon as it is formed. After purification, a good yield (30%) of the expected 3-methylquinazolin-4-one (**5**) was obtained. The process was optimized varying the amount of acetic anhydride (1, 2.5 and 5 equiv) and formamide (1, 2.5, 5 and 10 equiv) that were tested (Table 1). The best result was obtained when anthranilic acid and 2.5 equiv of acetic anhydride were mixed with 5 equiv of formamide. The influence of reaction time was also evaluated. Table 1 shows that 3 min of heating at 200 °C (200 W) gave the best yield whilst a longer heating (6, 8 or 10 min) seemed to decrease the yield and afforded most degradation products, difficult to identify.

The optimized conditions were used for the synthesis of products **6–8**, starting from various anhydrides (Scheme 2, Table 1). The lowest observed yield for compound **8** (25%) can be explained considering that benzoic anhydride being a powder, it induced a certain heterogeneity of the starting mixture making efficient

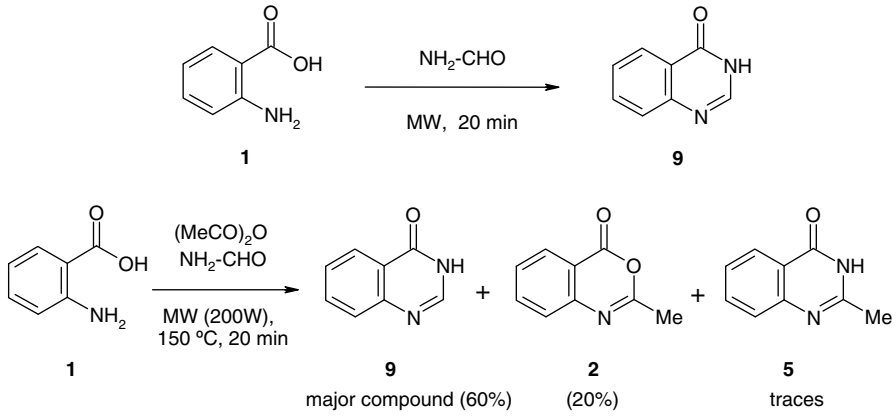
Table 1
Microwave experimental conditions

Reaction time (min)	Temperature (°C)	Power input (W)[a]	Product	Yield[b] (%)
1	200	200	**5**	18
2	200	200	**5**	45
3	200	200	**5**	52
6	200	200	**5**	36
8	200	200	**5**	30
10	200	200	**5**	30
3	170	200	**5**	17[c]
6	170	200	**5**	50[c]
6	150	200	**9**[d]	60
6	100	200	**5**	—[e]
3	200	200	**6**	55
3	200	200	**7**	62
3	200	200	**8**	25[f]
6	200	400	**6**	74
10	170	400	**6**	73

[a] 2 min (300 W) ramp + 1–10 min irradiation (200 W).
[b] Average yields after three experiments, at least.
[c] Presence of by-products (**2** and **9**) detected with variable yields.
[d] Traces of **5**.
[e] Starting material retrieved.
[f] Use of 10 equiv of formamide is necessary to allow better reaction homogeneity and convenient detection of temperature.



Scheme 2. Three-component synthesis of 2-substituted quinazolin-4(3*H*)-ones (**5**–**8**), conditions: carboxylic anhydride (2.5 equiv), formamide (5 equiv).



Scheme 3. Three microwave-assisted re-investigations of the Niementowski reaction.[14]

heating more difficult to achieve than for the other reactions. In this case, a certain improvement could be obtained with a higher quantity of formamide (10 equiv).

The synthesis of **6** was also explored on larger scale using the multimode-like scale-up capabilities of the MultiSYNTH® microwave platform. Thus, 12 reaction tubes containing each 0.5 g of the starting anthranilic acid, propionic anhydride (2.5 equiv) and formamide (5 equiv) were simultaneously irradiated at 200 °C (400 W) for 6 min. A convenient amount (5.2 g, 74% yield) of the expected quinazoline **6** was obtained after work-up. A comparable result was also obtained at 170 °C in longer time (10 min) as observed during optimization runs.

According to these results, we can confirm that decomposition of formamide under controlled reaction conditions can be an efficient source of ammonia to be introduced into heterocyclic rings like quinazolines.

Some years ago we described the microwave-assisted synthesis of the quinazolin-4-one skeleton via condensation of formamide with anthranilic acid[14] in an old process generally called the 'Niementowski reaction' (Scheme 3).[15] The last part of this Letter re-investigates the experimental design of this reaction. Our questions concern the stability of formamide under the conditions described in our previous paper. In fact, at that time, the reaction temperature was only controlled using an IR pyrometer and not a fibre-optic contact thermometer. This study was inspired by a recent study published by Kappe and his co-workers on the importance of internal temperature monitoring in microwave chemistry.[16] In our previous report, the best synthesis of the nude quinazolin-4-one **9** was obtained by treatment of anthranilic acid with 5 equiv of formamide with an irradiation programmed at 60 W and a fixed temperature of 150 °C, working at atmospheric pressure.

Working under pressure (in sealed vials) in the new hybrid MultiSYNTH® reactor, with the same conditions of power (60 W) and temperature (150 °C), gave a yield of 62% of the expected product which is lower than the value of 90% obtained before (Table 2). As we may now predict, working at a higher temperature (200 °C) needs more power (200 W) and gives lower yields of **9** (18%) and a final more messy reaction mixture. Irradiation at 100 °C (60 W) resulted in unreacted starting material. Considering that the temperature measurement can be different between IR pyrometer and fibre-optic, we increased the temperature of the reaction until 170 °C with a power of 200 W without changing the other parameters (amounts and time: 20 min). In this case, the yield of 90% was retrieved. Reduction of reaction time was also investigated without success. This result suggests that to work in sealed vials is not crucial for the success of these reactions and that the power input does have a specific influence on the reaction outcome. Nevertheless, a power of 200 W is required to achieve the optimum reaction temperature of 170 °C in an acceptable time avoiding too long ramp periods.

Back to the study described above we were curious to see the result of the three-component reaction under the new conditions described here. Thus, heating a mixture of anthranilic acid (**1**), acetic anhydride and formamide at 150 °C (60 W) for 20 min gave a major compound identified as the quinazolin-4-one **9** accompanied by variable amounts of benzoxazin-4-one **2** and traces of the 3-substituted quinazolin-4-one **5**. This result is convenient with a possible competition between the formation of **9** and **2**. The access to product **5** could be explained considering that a

Table 2
Microwave experimental conditions for the synthesis of **9**

Reaction time (min)	Temperature (°C)	Power input (W)[a]	Product	Yield[b] (%)
20	150	60	**9**	90[a]
20	150	60	**9**	62
20	100	60	**9**	—[b]
20	170[c]	200	**9**	90

[a] Realized at atmospheric pressure in a CEM Discover® apparatus, temperature measured by IR pyrometer.
[b] Starting material retrieved.
[c] 2 min (300 W) ramp + 10 min irradiation (200 W), internal temperature measured by fibre-optic.

certain amount of formamide may decompose under the used experimental conditions and react with the formed benzoxazin-4-one.

In conclusion, we have demonstrated here that microwave-assisted rapid decomposition of formamide can be favourably used as an inexpensive and easy to handle ammonia source for the synthesis of nitrogen-containing heterocyclic rings. Our results can also be considered as examples of the real specific effect of microwaves consisting in the capacity to specifically interact with molecules according to their dielectric properties. Microwave technology offers to chemists the possibility of a full control of all reaction parameters with operational, economical and environmental benefits over conventional methods.

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