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Microwave-assisted Niementowski reaction. Back to the roots

François-René Alexandre,[a,b] Amaya Berecibar[a] and Thierry Besson[b,*]

[a]*PFIZER Global Research & Development, Fresnes Laboratories, 3–9 rue de la Loge, BP100, F-94265 Fresnes cedex, France*
[b]*Laboratoire de Génie Protéique et Cellulaire, EA3169, Groupe de Chimie Organique, UFR Sciences Fondamentales et Sciences pour l'Ingénieur, Bâtiment Marie Curie, Université de la Rochelle, F-17042 La Rochelle cedex 1, France*

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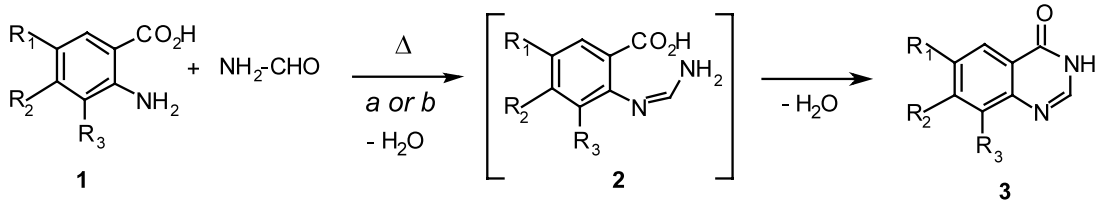
Abstract—In a search to speed up an aspect of the drug discovery processes, the Niementowski synthesis of the 3*H*-quinazolin-4-one core was reinvestigated using microwave irradiation. The experimental methodology and microwave conditions described here are well established, allowing significant rate enhancements and good yields compared to conventional reaction conditions.

The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities.[1]

In the course of our work on the preparation of new polyheterocyclic systems with pharmaceutical value, we recently described the synthesis of novel heterocycles in which the quinazoline ring was fused with thiazole, indole or benzimidazole rings.[2] Following such a strategy, we planned to prepare 3*H*-quinazolin-4-one derivatives which can be employed as intermediates in the synthesis of useful bioactive compounds. Quinazolin-4-ones have not been the object of new synthetic developments in the last few years and recent reports on their preparation use only classical procedures.[3] The most common synthetic method of the 3*H*-quinazolin-4-one ring is based on the Niementowski reaction,[4] which involves the fusion of anthranilic acid (or a derivative, e.g. 2-aminobenzonitrile) with formamide and proceeds usually via an *o*-amidine intermediate (Scheme 1). This procedure usually needs high temperatures and requires lengthy and tedious conditions.

Microwave irradiation is known to allow a striking reduction in reaction times, good yields and cleaner reactions than the purely thermal procedures. Our previous experience in the use of microwave in organic synthesis,[5] led us to check if there was any possibility for improvement in the Niementowski method used for the synthesis of the quinazoline skeleton.[6] In this paper, we report the benefits associated with this new methodology and we identify standard experimental conditions.

Following the strategy originally published by Niementowski,[4] synthesis of the 3*H*-quinazolin-4-one ring involves long heating (several hours) of the anthranilic acids with an excess of formamide at 130–150°C. The amount of quinazolines obtained in such conditions is



Scheme 1. The Niementowski reaction:[4] (a) conventional conditions: 130–150°C, average time 6 h; (b) microwave conditions: MW (60 W), 150°C, average time 20 min.

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* Corresponding author. Tel.: +33 (0)5 46 45 82 76; e-mail: tbesson@univ-lr.fr

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Table 1. Synthesis of 3*H*-quinazolin-4-ones from various anthranilic acids[7,9]

Starting material	R_1	R_2	R_3	Reaction time (min)	Product	Yield (%)	Mp (°C) (lit.[8])
1a	H	H	H	20	**3a**	90[a]	216[b] (215)
1b	Me	H	H	15	**3b**	75	259[b] (260–261)
1c	Br	H	H	20	**3c**	75	262[b] (261–267)
1d	NO_2	H	H	20	**3d**	87	>260[c] (286)
1e	OMe	OMe	H	40	**3e**	70	>260[d] (296–297)
1f	Br	H	Br	15	**3f**	78	>260[e] (295–296)
1g	OH	H	H	15	**3g**	86	>260[e] (>300)
1h	OMe	OMe	OMe	40	**3h**	77	231[b] (226–227)
1i	$-C_2H_4-$		H	15	**3i**	77	>260[e] (273–274)
1j	Pyridine[f]			20	**3j**	80	258[e] (258)

[a] A conventional thermal heating (oil bath) of this reaction at 150°C for 6 h led to the expected product in a 59% yield.
[b] From EtOH.
[c] From MeOH.
[d] Not recrystallized.
[e] From H_2O.
[f] Starting material: 2-aminonicotinic acid.

variable and sometimes low yields were observed accompanied by complicated mixtures of carbonaceous compounds and impurities which were difficult to eliminate, even by column chromatography or recrystallization.

As we previously mentioned in similar studies, transposing such a reaction under focused microwave irradiation needs special attention. For this reason we performed preliminary experiments in order to establish the best experimental conditions.

(a) Irradiation power and temperature: condensation of anthranilic acid with formamide was performed at various temperatures (120–170°C) (with a power control) or at varying power (with infrared measurement of the temperature reached in the mixture). A control of the irradiation power and a fixed temperature led to better yields and good experimental conditions.

(b) Heterogeneous or homogeneous mixtures: association of liquid/solid reactants may involve uncontrolled reactions and is generally worse than in comparative thermal reactions. As we previously published in similar reactions, in the present study, experiments in which the starting compounds were mixed on graphite led to heterogeneous mixtures and resulted in poor yields and hazardous bumping in the reactor. The best alternative is to work with an excess of formamide as fusion accelerator (by itself formamide is a good candidate for microwave heating).

(c) Reactants: the ratio between the quantity of formamide and anthranilic acid is very important. If it is too small, lower yields were observed, probably due to the resulting heavy syrup or gum which made the work-up more difficult.

Among the various combinations tested, the best results were obtained by treatment of the anthranilic acid with 5 equiv. of formamide with an irradiation programmed at 60 W and a fixed temperature (150°C). Here again the comparative study of this procedure by classical heating (oil bath) and microwave irradiation showed that reaction time was reduced from several hours to few minutes (Scheme 1) by using the latter technique. This process was extended to various anthranilic acids to give the desired products in very good yields (Table 1). Here again no by-products were detected and reactions were cleaner than for the purely thermal procedures.

In conclusion we have reinvestigated the original work by von Niementowski under microwave irradiation. Using dedicated microwave instruments this reaction could be easily and rapidly performed in very good yields, providing a large quantity of various quinazolin-4-ones which can be employed as intermediates in the synthesis of useful bioactive compounds. We have also demonstrated that previously difficult and traditional transformations can now be rapidly and safely completed by microwave irradiation.

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6. Only one example of the synthesis of the quinazoline ring via a modified Niementowski reaction was recently described: anthranilic acid and formanilide were mixed in the presence of *N*,*N*-dimethylacetamide. See: Rad-Moghadam, K.; Khajavi, M. S.; *J. Chem. Res. (S)* **1998**, 702–703.
7. Focused microwave irradiations were carried out at atmospheric pressure with a CEM Discover™ focused microwave reactor (300 W, monomode system) which has in situ magnetic variable speed, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control. Equipment of the oven was completed by a condenser allowing conditions close to those involved in classical methods; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 bar) if necessary.
8. Ref. for compound **3**: (a) **3a**, **3e**, **3g**: Le Mahieu, R. A.; Carson, M.; Nazon, W. C.; Parrish, D. R.; Welton, A. F.; Baruth, H. W.; Yaremko, B. *J. Med. Chem.* **1983**, *26*, 420–425; (b) **3b**, **3c**, **3d**, **3f**: Baker, B. R.; Schaub, Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 141–148; (c) **3h**: Gavit, A.; Chen, J.; App, H.; McMahon, G.; Hirth, P.; Chen, I.; Levitzki, A. *Bioorg. Med. Chem.* **1996**, *4*, 1203–1208; (d) **3i**: Baker, B. R.; Schaub, Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 149–156; (f) **3j**: Robins, R. K.; Hitchings, G. H. *J. Am. Chem. Soc.* **1955**, *77*, 2256–2260.
9. Typical procedure for the synthesis of **3a**: A mixture of anthranilic acid (1 g, 7.3 mmol) and formamide (1.45 mL, 36.5 mmol) was irradiated at 150°C (power input: 60 W) until completion (TLC monitoring, 20 min). After cooling the reaction mixture was rinsed out with ethyl acetate and evaporated under reduced pressure. Recrystallization from ethanol afforded quinazolin-4-one **3a** as a white solid (960 mg, 90%).

Spectroscopic data for compounds **3**: Quinazolin-4(3*H*)-one **3a**: MS (ESI, El$^+$) m/z 147 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 7.49 (dt, 1H, J=8.1, 1.0 Hz), 7.64 (d, 1H, J=8.1 Hz), 7.78 (dt, 1H, J=8.1, 1.5 Hz), 8.07 (s, 1H), 8.10 (dd, 1H, J=8.1, 1.5 Hz), 12.29 (brs, 1H); 6-methylquinazolin-4(3*H*)-one **3b**: MS (ESI, El$^+$) m/z 161 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 7.55 (d, 1H, J=8.4 Hz), 7.62 (dd, 1H, J=8.4, 2.0 Hz), 7.90 (d, 1H, J=2.0 Hz), 8.01 (s, 1H), 12.16 (brs, 1H); 6-bromoquinazolin-4(3*H*)-one **3c**: MS (ESI, El$^+$) m/z 225/227 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 7.61 (d, 1H, J=8.8 Hz), 7.95 (dd, 1H, J=8.8, 2.0 Hz), 8.13 (s, 1H), 8.17 (d, 1H, J=2.0 Hz), 12.45 (brs, 1H); 6-nitroquinazolin-4(3*H*)-one **3d**: MS (ESI, El$^-$) m/z 190 (M–H$^+$); ^{1}H NMR (DMSO-d_6) δ 7.83 (d, 1H, J=8.8 Hz), 8.29 (s, 1H), 8.51 (dd, 1H, J=8.8, 2.8 Hz), 8.76 (d, 1H, J=2.8 Hz), 12.75 (brs, 1H); 6,7-dimethoxyquinazolin-4(3*H*)-one **3e**: MS (ESI, El$^+$) m/z 207 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 3.89 (s, 3H), 7.12 (s, 1H), 7.43 (s, 1H), 7.98 (s, 1H), 12.06 (brs, 1H); 6,8-dibromoquinazolin-4(3*H*)-one **3f**: MS (ESI, El$^+$) m/z 304/308 (M–H$^+$); ^{1}H NMR (DMSO-d_6) δ 8.17 (d, 1H, J=2.4 Hz), 8.24 (s, 1H), 8.34 (d, 1H, J=2.4 Hz), 12.67 (brs, 1H); 6-hydroxy-4(3*H*)-quinazolin-4(3*H*)-one **3g**: MS (ESI, El$^+$) m/z 163 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 7.43 (dd, 1H, J=8.8, 2.8 Hz), 7.39 (d, 1H, J=2.8 Hz), 7.52 (d, 1H, J=8.8 Hz), 7.89 (s, 1H), 10.07 (brs, 1H), 12.02 (brs, 1H); 6,7,8-trimethoxy-4(3*H*)-quinazolin-4(3*H*)-one **3h**: MS (ESI, El$^+$) m/z 237 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 3.88 (s, 3H), 23.93 (s, 3H), 7.33 (s, 1H), 7.99 (s, 1H), 12.18 (brs, 1H); benzo[*g*]quinazolin-4(3*H*)-one **3i**: MS (ESI, El$^+$) m/z 197 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 7.58 (m, 1H), 7.66 (m, 1H), 8.84 (m, 2H), 8.21 (m, 2H), 12.06 (brs, 1H); pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3j**:MS (ESI, El$^+$) m/z 148 (MH$^+$); ^{1}H NMR (DMSO-d_6) δ 7.54 (dd, 1H, J=7.8, 4.4 Hz), 8.30 (s, 1H), 8.49 (dd, 1H, J=7.8, 2.0 Hz), 8.94 (dd, 1H, J=4.4, 2.0 Hz), 12.55 (brs, 1H).