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Convenient one-pot synthesis of N^3-substituted pyrido[2,3-*d*]-, pyrido[3,4-*d*]-, pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones, and quinazolin-4(3*H*)-ones analogs

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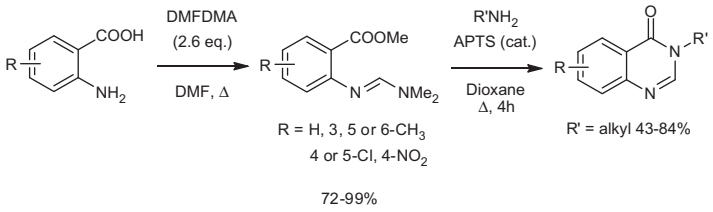
One-pot sequential synthesis

ABSTRACT

A convenient microwave-assisted one-pot sequential synthesis provided access to novel pyridopyrimidin-4-(3*H*)-ones in good to excellent yields. Anthranilic acid, 2- and 4-aminonicotinic acids, and 3-aminoisonicotinic acid were quantitatively converted into the analogous amidinoesters which undergo rapid cyclization in the presence of an amine.

The main interests of our research group include the synthesis of C,N,S-containing heterocyclic precursors of bioactive molecules able to modulate the role of kinases in signal transduction.[1] As part of this work, the syntheses of various quinazoline derivatives were described.[2] Among all the studied compounds, N^3-susbtituted quinazolines were particularly studied and their synthesis has been the focus of a large part of our efforts for 10 years. The biological activity of such derivatives[3] incited us to extend recent investigations to novel pyridopyrimidine analogs with the aim of carrying out further structure-activity relationship studies. The main part of the chemistry performed in this study was achieved under microwave irradiation as a continuation of our global strategy which consists to design adapted reactants and techniques offering operational, economic, and environmental benefits over conventional methods. This Letter describes the development of a reliable and simple method that allows the preparation of a small library of novel pyridopyrimidine derivatives for which interesting biological properties can be expected.

The first part of this work was inspired by Foster and co-workers who described a preliminary study dealing with the synthesis of N^3-susbstituted quinazolin-4-ones. The authors demonstrated that the bicyclic compounds can be readily synthesized from substituted anthranilic acids by treatment with dimethylformamide-dimethylacetal (DMFDMA), followed with acid-catalyzed cyclization of the intermediate formamidinoester by attack of an aliphatic amine (Scheme 1).[4]



Scheme 1. Conditions described for the synthesis of N^3-substituted quinazolines using DMFDMA.[4]

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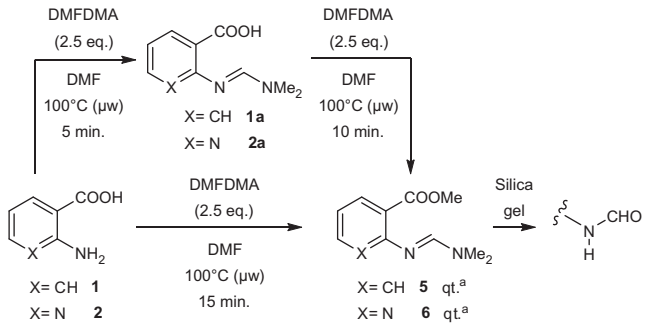
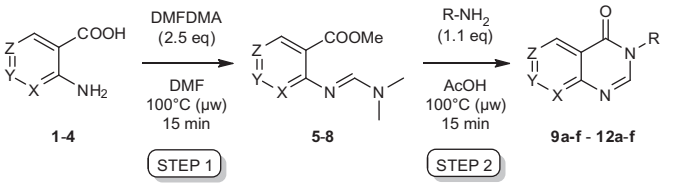


Scheme 2. Conversion of anthranilic acid **1** and 2-aminonicotinic acid **2** into their amidinoester analogs **5** and **6**. [a]Determined by ^{1}H NMR of the crude mixture.



X, Y, Z = CH; **1** (anthranilic acid), **5, 9**
X = N; Y, Z = CH; **2** (2-aminonicotinic acid), **6, 10**
X = CH; Y = N; Z = CH; **3** (3-aminoisonicotinic acid),**7,11**
X, Y = CH; Z = N; **4** (4-aminonicotinic acid chlorhydrate), **8, 12**

Scheme 3. Optimized protocol for the one-pot synthesis of 3-substituted quinazolin-4(3*H*)-ones (**9**), pyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones (**10**), pyrido[3,4-*d*]-pyrimidin-4(3*H*)-ones (**11**), and pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones (**12**). 4-Aminonicotinic acid chlorhydrate **4** required 3 equiv of DMFDMA for completion of step 1; for yields see Table 2.

Table 1
Evolution of the ratios of starting acids (**1** and **2**), amidinoacids (**1a** and **2a**), and amidinoesters (**5** and **6**)

Reaction time[a] (min)	**1**:**1a**:**5** Ratio[b]	**2**:**2a**:**6** Ratio[b]
5	0:0.86:0.14	0:0.83:0.17
10	0:0.36:0.64	0:0.17:0.83
15	0:0:1[c]	0:0:1[c]

[a] Reaction time does not include temperature ramp of 2 min.
[b] Determined by ^{1}H NMR of the crude mixture.
[c] Quantitative yield.

Purification of the intermediate compounds revealed to be very tricky (Kügelrohr distillation at reduced pressure) due to the high instability of the intermediate amidinoesters which may possibly undergo hydrolysis to give rise to the corresponding formylesters.

Considering on-going experiments using DMFDMA for the microwave-assisted synthesis of 4-substituted quinazolines via Dimroth rearrangement[2] and pyrimidin-4-amines via formamide degradation,[5,6] we decided to focus our first efforts on an efficient one-pot multi-component reactant (MCR) synthesis of quinazolin-4-ones and extend to original pyridopyrimidin-4-one derivatives themselves obtained from aminonicotinic acid analogs (**1**–**4**; see Scheme 3). Both steps of this new sequential synthesis were carried out in a microwave oven allowing a strict control of the reaction conditions as described in previous works.[2]

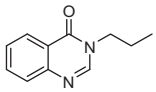
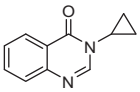
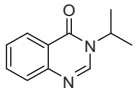
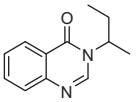
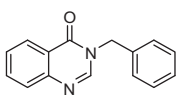
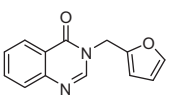
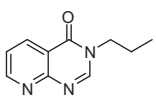
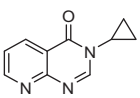
Optimization of the reaction conditions proved that at least 15 min of irradiation are necessary for the concomitant formation of both amidine and ester functions in DMF when anthranilic acid **1** and 2-aminonicotinic acid **2** were used. Carrying out this experiment without DMF led to a complex mixture of carbonaceous compounds. Various conditions of chromatographic purifications were tested (silica and alumina gels) and demonstrated that the intermediate amidinoesters **5** and **6**, were in fact completely transformed into unexpected N-formylated analogs (Scheme 2).

A kinetic study of this first step in the case of **1** and **2** showed that the amino function of the starting material was formylated in 5 min, prior to the esterification process and no starting acid remained after 5 min (Table 1).

As a result of this preliminary study, a reaction first involving the formation of the amidinoester followed with the cyclization would best suit our needs for a new process giving access to the desired compounds. Thus, in the hope to implement a one-pot synthesis of N^3-substituted quinazolin-4(3*H*)-ones by means of a formylation/esterification/cyclization sequence, a MCR procedure was initiated with starting anthranilic acid, DMFDMA, and benzylamine, but failed to give the cyclized product.

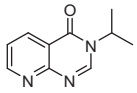
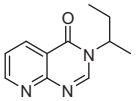
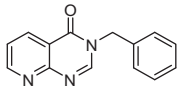
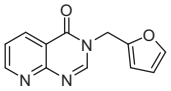
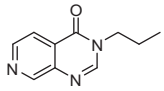
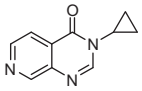
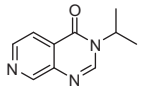
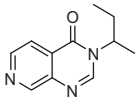
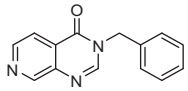
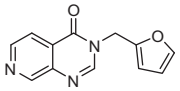
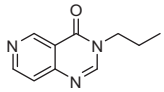
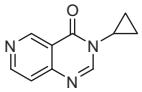
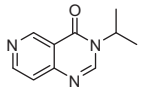
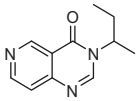
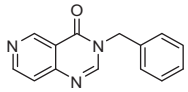
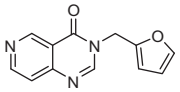
Pursuing our effort, it was decided to operate via a one-pot sequential strategy which consisted in performing the first step as described above, namely irradiation of the starting anthranilic acid **1** and DMFDMA in DMF for 15 min at 100 °C. Once the solvent (DMF) was eliminated, the amine and acetic acid were immediately added in the reaction flask and irradiated at 100 °C for further 15 min. As depicted in Table 2 various amines could be used affording N^3-alkylated quinazolin-4-ones **9a**–**f** in good to excellent yields within a short period of time (Scheme 3).

Table 2
Isolated yields for the one-pot synthesis of 3-substituted quinazolin-4(3*H*)-ones (**9a**–**9f**), pyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones (**10a**–**10f**), pyrido[3,4-*d*]-pyrimidin-4(3*H*)-ones (**11a**–**11f**), and pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones (**12a**–**12f**)

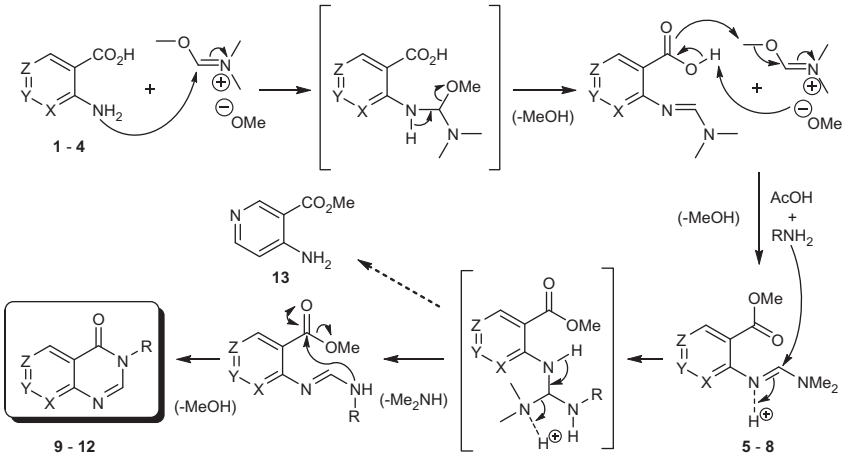
Product	Formula	Yield[a] (%)	Product	Formula	Yield[a] (%)
9a		87	**9b**		82
9c		70	**9d**		87
9e		98	**9f**		83
10a		88	**10b**		84

(*continued on next page*)

Table 2 (*continued*)

Product	Formula	Yield[a] (%)	Product	Formula	Yield[a] (%)
10c		82	**10d**		89
10e		98	**10f**		97
11a		86	**11b**		83
11c		77	**11d**		82
11e		86	**11f**		63
12a		67	**12b**		41
12c		48	**12d**		54
12e		63	**12f**		58

[a] Isolated yield.



Scheme 4. Proposed mechanism for the synthesis of 3-substituted quinazolin-4(3*H*)-ones (**9**), pyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones (**10**), pyrido[3,4-*d*]-pyrimidin-4(3*H*)-ones (**11**), and pyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones (**12**).

Pleasingly, the same reaction sequence could be successfully conducted with 2-aminonicotinic acid **2**, 3-isonicotinic acid chlorhydrate **3**, and 4-aminonicotinic acid **4** in the presence of a range of amines to afford, in good to excellent yields, the corresponding pyrido[2,3-*d*]pyrimidin-4-ones (**10a**–**f**), pyrido[3,4-*d*]pyrimidin-4-ones (**11a**–**f**), and pyrido[4,3-*d*]pyrimidin-4-ones (**12a**–**f**), respectively (Table 2).

Results collected in Table 2 demonstrated that the yields obtained with a given amine are mostly influenced by the position of the pyridine nitrogen. It appears that those yields decreased with the *ortho*, *meta*, and *para* position of the formamidine function to the intracyclic nitrogen.

Considering the kinetic study of the first step, attack of the aromatic amine (**1**–**4**) on the most electrophilic site of the iminium methoxide salt was completed in 5 min. Methoxide anion thus released then trapped the carboxylic acid proton, allowing the corresponding carboxylate to attack the second electrophilic site of the iminium salt, affording the formimidamidoesters (**5**–**8**) in quantitative yields. The mechanism of cyclization occurred via a first attack of the amine on the activated carbon of the amidine. The

intermediate triamine species released dimethylamine and cyclized into the expected quinazolines (**9a**–**f**) and pyridopyrimidines (**10a**–**f** to 1**2a**–**f**). In the specific case of 4-aminonicotinic acid **4**, the low yields observed can be explained by a substantial contribution of a zwitterionic resonance form which could involve the instability of the intermediate triamine resulting from the condensation of the primary amine on the formimidamidoester **8**. The elimination process turned in favor of the unexpected aminoester (see **13** Scheme 4) which was isolated in 15–20% yield. This deactivation was not significant with 2-aminonicotinic acid **2** since the contribution of the analogous zwitterionic resonance form was considerably less important.[7]

Some comments can be made concerning the microwave procedure as well as the technical and practical aspects.[8] In the case of our microwave-assisted synthesis, DMF and acetic acid present the advantage of having good dielectric properties, thus giving an efficient heating of the reaction mixture.[9] A reactor able to work at atmospheric pressure had some advantages, such as the possibility of easier work-up and the use of common laboratory glassware. In the main steps of the synthetic pathway described in this Letter, irradiation power at 900 W was enough to efficiently reach the programmed temperature with a short time ramp (2 min, not added to the reaction time indicated in schemes). Temperature was monitored via a contactless-infrared pyrometer which was calibrated by control experiments with a fiber-optic contact thermometer.

In conclusion, the highlight of this work is the development of a convenient one-pot sequential process which was perfectly controlled using microwave technology at atmospheric pressure. Thus, the syntheses of various N^3-alkylated quinazolin-4-ones (**9a**–**f**), and novel pyrido[2,3-*d*]pyrimidin-4-ones (**10a**–**f**),[10] pyrido[3,4-*d*]pyrimidin-4-ones (**11a**–**f**) and pyrido[4,3-*d*]pyrimidin-4-ones (**12a**–**f**), were optimized in a reliable and simple method which can be applied to various ring systems and amines in order to constitute libraries of chemical scaffolds.

Acknowledgments

Financial support from the MESR (Ministere de l'Enseignement Superieur et de la Recherche) is gratefully acknowledged for the doctoral fellowships to D.H. We thank the LABEX SynOrg (ANR-11-LABX-0029) and AI-Chem Channel program for financial support. We also acknowledge Milestone S.r.l. (Italy) for provision of the microwave reactors and technical support.

Supplementary data

Supplementary data (experimental procedures, ^{1}H and ^{13}C NMR spectra of products **9a**–**f**, **10a**–**f**, **11a**–**f**, **12a**–**f**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.096.

References and notes

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8. Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. RotoSYNTHTM (Milestone S.r.l. Italy) is a multi-mode cavity with a microwave power delivery system ranging from 0 to 1200 W. Open vessel experiments were carried out in 50 or 100 mL round bottom flasks fitted with a reflux condenser. Temperature was monitored via a contactless-infrared pyrometer which was calibrated by control experiments with a fiber-optic contact thermometer. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature, pressure, and power profiles were monitored in both cases through the EASY-Control software provided by the manufacturer.
9. Lost dissipation factor (tan δ) expresses the capacity of a molecule or a material to transform electromagnetic energy into thermal energy. A very high susceptibility to microwaves is characterized by a high value (>0.5) of tan δ. Tan δ (acetic acid) = 0.174 at 2.45 GHz. For more details see: Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–224.
10. Except for compounds **10e** and **10f** (previously described in: Hou, G.; Gravier, D.; Casadebaig, F.; Dupin, J.-P.; Bernard, H.; Boisseau, M. *Pharmazie* **1995**, 50, 719–722) all the pyridopyrimidin-4-ones **10a**–**d**, **11a**–**f** and **12a**–**f** described in this paper can be considered as new products.