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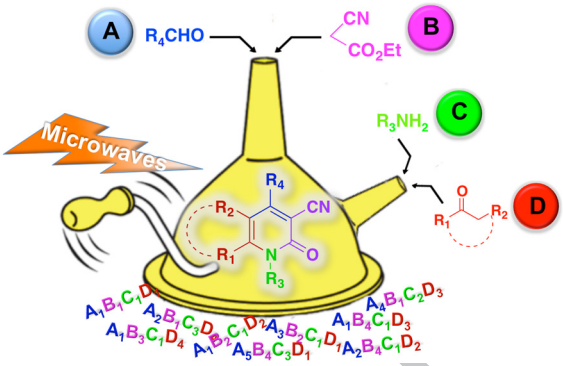

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ABSTRACT

A fast, versatile and practical one-pot, two-step microwave-assisted protocol for the direct synthesis of N1-substituted 5,6-ring-fused 2-pyridones has been developed. The present method proved to be effective on a series of commercially available aldehydes, ketones and amines and could be profitably exploited in drug-discovery settings for the rapid identification of biologically relevant hit compounds.

Nitrogen-containing heterocycles represent a wide class of organic molecules broadly distributed in nature and often endowed with attracting biological properties. Within this class, 2-pyridones represent ubiquitous scaffolds frequently found in natural products and pharmaceutical compounds (Figure 1). 2-Pyridone analogues are currently used in the treatment of congestive heart failure (Amrinone and Milrinone),[1] idiopatic pulmonary fibrosis (Pirfenidone)[2] or as antitumor agents (Topotecan).[3] Other representative ring-fused 2-pyridones are reported as acetylcholinesterase inhibitors (Huperzine A),[4] PARP-1 inhibitors (PJ34)[5] and anti-HIV agents (INDOPY-1)[6] (Figure 1). Due to their wide application in medicinal chemistry, it is not surprising that the synthesis of 2-pyridone derivatives has attracted organic chemists for many years, and several effective procedures for the synthesis of highly functionalized derivatives are continuously being developed.[7] Depending on the required molecular complexity, different approaches can be employed for the synthesis of the 2-pyridones: while multistep protocols usually allow one to obtain a higher degree of chemical diversity around the heterocyclic core, multicomponent approaches present the advantage of atom- and cost-efficiency that, coupled with microwaves techniques, may allow one to quickly generate new chemical entities for drug discovery purposes.[8]

The classical multistep approach for the synthesis of substituted 2-pyridones requires the conversion of 4-hydroxy-6-methylpyran-2-one into 4-hydroxy-6-methylpyridin-2-one followed by C4 O-alkylation and N1-alkylation.[9] Although a wide range of alkylating agents could be employed, further functionalization at positions C3 and C5 requires additional synthetic steps, and often the use of hazardous reagents. Among the available multistep strategies,[10] Kibou et al. recently reported a solvent-free protocol comprising a Knoevenagel condensation of ethyl cyanoacetate with acetophenones, followed by formation of an enaminonitrile intermediate which was finally cyclized in presence of a primary amine to give 1,3,4-substituted 2-pyridones.[11] This approach worked well with a wide range of reactants, but allowed access to 5,6-unsubstituted derivatives only. In recent years, a few interesting multicomponent approaches for the synthesis of substituted 2-pyridones have also been developed.[12] Sun et al. reported a domino reaction of arylamines, methyl propiolate, aromatic aldehydes and ethyl cyanoacetate, in the presence of catalytic triethylamine, to give 1,3,4,5-substituted 2-pyridones in moderate yields after stirring

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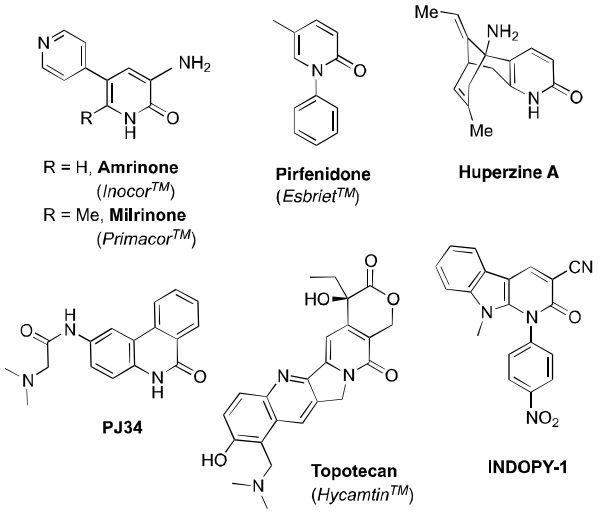
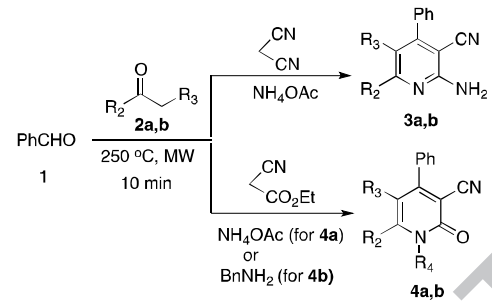


Figure 1. Representative 2-pyridone-based bioactive compounds

for 24 hours.[13] Yermolayev et al. developed a one-pot three-step microwave-assisted method for the synthesis of N1-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitrile derivatives[14] while several authors reported the preparation of 3,4,6-substituted 2-pyridones via one-pot reaction between ketones (generally acetophenones), aldehydes (generally aromatic), ammonium acetate and ethyl cyanoacetate.[15] Although the latter approach is the most utilized for the synthesis of biologically relevant compounds, its application to the development of ring-fused 2-pyridones is poorly investigated and limited to N1-unsubstituted derivatives. With the aim to develop a versatile synthetic protocol for the direct synthesis of N1-functionalized ring-fused 2-pyridones and as a continuation of our interest in microwave methodologies for the synthesis of new heterocycles,[16] herein we describe the development of a microwave-assisted one-pot, two-step protocol for the synthesis of 1,3,4-substituted 5,6-ring-fused 2-pyridones.

Our preliminary experiments were inspired by the work published in 2005 by Shi, et al.,[17] which reported the multicomponent synthesis of 2-amino-3-cyanopyridine derivatives without solvent in a domestic microwave oven. The results obtained by Shi and colleagues were initially reproduced in a microwave oven for organic synthesis, reacting benzaldehyde **1** with malononitrile and acetophenone **2a** in the presence of ammonium acetate at 250 °C in open vessel mode (Scheme 1, Table 1). Compound **3a** was thus obtained after 10 minutes in 80% yield. The same protocol was then applied to cyclic ketones: substitution of acetophenone **2a** with cyclohexanone **2b** led to the ring-fused derivative **3b**, even if with low yields. To obtain the corresponding ring-fused 2-pyridones, benzaldehyde **1**, ethylcyanoacetate, cyclohexanone **2b** and ammonium acetate were reacted under the above reported conditions but only traces of compound **4a** were identified. We also tried to replace ammonium acetate with a primary amine to obtain the desired 1,3,4-substituted 5,6-ring-fused 2-pyridones. Unfortunately, when benzylamine was used in this multicomponent protocol, a very complex mixture was obtained and **4b** was never isolated. A systematic study of this multicomponent reaction with the aim of obtaining the desired N1-substituted 5,6-ring-fused 2-pyridones was undertaken. Based on the reaction mechanism proposed by Shi et al.,[16] we decided to divide the reaction in two consecutive steps in the same



Scheme 1. Application of the standard multicomponent procedure.

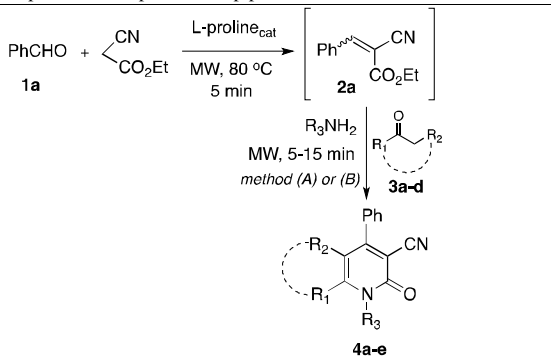
Table 1. Multicomponent synthesis of 2-aminopyridines and 2-pyridones

Cpd.	R_2	R_3	R_4	Yield[a](%)
3a	Ph	H	-	80
3b			-	20
4a			H	Trace
4b			Bn	-

[a]Isolated yield

reaction vessel to better control the outcome of the individual reactions: in the first step, the aldehyde and the ethyl cyanoacetate were reacted to afford the Knoevenagel adduct; in the second step, the in-situ generated imine (from the added ketones and amines) cyclized with the alkylidene produced in the first step to give the final 2-pyridone. The reaction conditions were initially optimized for the synthesis of compounds **4a** and **4b**, used as model reactions to prepare N1-unsubstituted and N1-substituted derivatives, respectively. Different solvents (DME, EtOH, *t*-BuOH, DMF), catalysts (Et_3N, piperidine, $AlCl_3$, L-proline) temperatures and reaction times were used in both steps. After several attempts, the best reaction conditions for the first step were found to be those employing L-proline as a catalyst in solvent-free, microwave-assisted conditions. The optimal reaction conditions for the second step varied depending on the nature of the amines used: ammonium acetate (Method A) or primary amines (Method B). In the optimized model reaction (Table 2), benzaldehyde **1a** and ethyl cyanoacetate were irradiated, in the presence of catalytic L-proline, for 5 minutes at 80 °C in a microwave sealed tube to quantitatively obtain the arylidene **2**.

Table 2. Optimized one-pot, two-step protocol

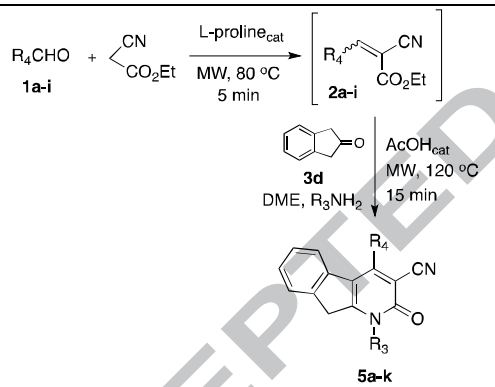


Entry	Cpd.	R_2, R_1	R_3	Method	Yield[a](%)
1	**4a**		H	A[b]	44
2	**4b**		Bn	B[c]	35
3	**4c**		Bn	B	33
4	**4d**		Bn	B	36
5	**4e**		Bn	B	45

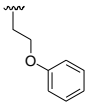
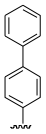
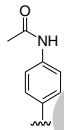
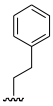
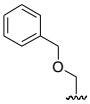
[a]Isolated yield. [b]Method A: neat, 200 W, 5 min; $R_3NH_2 = NH_4OAc$. [c]Method B: DME, 120 °C, 15 min, $AcOH_{cat}$; R_3NH_2 = benzylamine.

Cyclohexanone **3a** and ammonium acetate (Method A) were then added and the resulting mixture was heated in the microwave (200 W) for additional 5 minutes: the desired 5,6-fused pyridone **4a** was isolated as a pure product after a simple precipitation by addition of diethyl ether (Table 2, entry 1). Under optimized conditions for Method B, dimethoxyethane (DME), ketone (**3a-d**), catalytic acetic acid and benzylamine were added to the ice-cooled arylidene **2** and the reaction mixture was irradiated at 120 °C for 15 minutes. The desired N1-substituted 5,6-ring-fused 2-pyridones (**4b-e**) were obtained in moderate to good yields after chromatographic purification (Table 2, entries 2-5). It should be noted that similar 1,3,4,5,6-functionalized 2-pyridones are usually obtained with comparable overall yields after several synthetic steps,[11,18] while our approach

Table 3. N1-substituted 5,6-ring-fused 2-pyridone analogues



5a-k

Entry	Cpd.	R_4	R_3	Yield[a](%)
1	**5a**			30
2	**5b**			32
3	**5c**			50
4	**5d**			35
5	**5e**			30
6	**5f**			65
7	**5g**			35
8	**5h**			25
9	**5i**			34
10	**5j**	nPr-		20
11	**5k**	H		35

[a]Isolated yield.

provided the desired compounds after a 20 minutes reaction followed by a chromatographic purification. Under classical heating conditions, the optimized one-pot two-step protocol allowed to obtain compound **4e** in comparable yields (40%) but after longer reaction times (1h for the first step and 12h for the second step). To verify the versatility and efficiency of the optimized microwave-assisted one-pot, two-step protocol, a series of commercially available aldehydes (R_1CHO) and primary amines (R_4NH_2) were used as building blocks in the reaction with 2-indanone **3d** to generate a collection of 1,4-substituted 2,9-dihydro-2-oxo-*1H*, *2H*, *9H*-indeno[2,1-*b*]pyridine-3-carbonitrile derivatives **5a-k** (Table 3). In a first set of experiments, benzaldehyde **1a** was reacted, under the above reported optimized conditions (Method B), with ethyl cyanoacetate, 2-indanone **3d** and a series of amines (instead of the previously used benzylamine) that could also allow a subsequent elongation of the N1-chain (Table 3): propargylamine (Entry 1) gave product **5a**, that could be further elaborated via click-chemistry reaction; 2-aminoethanol (Entry 2) gave product **5b**, that could be further elongated via O-alkylation; phenoxyethylamine (Entry 3) gave product **5c** in good yields. Anilines did not react under the optimized reaction conditions. In a second set of experiments, different aldehydes **1a-i** were reacted in the one-pot, two-step protocol with ethyl cyanoacetate, 2-indanone **3d** and benzylamine to give a series of 4-substituted 1-benzyl-2-oxo-2,9-dihydro-1*H*-indeno[2,1-*b*]pyridine-3-carbonitriles **5d-j** (Table 3, Entries 4-10). The synthetic protocol proved to be effective with

aromatic aldehydes (Entries 4-5), heteroaromatic aldehydes (Entries 6-7) and different aliphatic aldehydes (Entries 8-10). Details on the synthetic procedures and compounds' characterization are reported in the Supplementary Material. Finally, it is interesting to note that para-formaldehyde (Entry 11) can be used in place of aromatic/aliphatic aldehydes to access C4-unsubstituted derivatives (e.g. **5k**) that, to the best of our knowledge, have never been obtained with a multicomponent procedure, but only after several synthetic steps. Additional experiments are ongoing in our laboratory to evaluate the versatility of this para-formaldehyde-based procedure and will be reported in due course.

In summary, a fast and versatile microwave-assisted one-pot two-steps protocol for the synthesis of N1-substituted 5,6-ring-fused 2-pyridones has been developed. Different reaction conditions were optimized depending on the nature of the reacted amines: using ammonium acetate (Method A), N1-unsubstituted 5,6-ring-fused 2-pyridones were obtained while using primary amines (Method B), N1-substituted 5,6-ring-fused 2-pyridones were generated. The present method can be used for the generation of N1-substituted 2-pyridones starting from commercially available aldehydes, ketones and amines in only 10 to 20 minutes and could be profitably exploited in drug-discovery settings for the rapid identification of biologically relevant hit compounds.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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