A ONE-POT TWO-STEP MICROWAVE-ASSISTED SYNTHESIS OF N1-SUBSTITUTED 5,6-RING-FUSED 2-PYRIDONES

Marco Radi*, Gian Paolo Vallerini, Alessia Petrelli, Sabrina Tassini, Paolo Vincetti and Gabriele Costantino

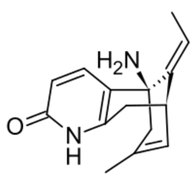
Dipartimento di Farmacia, Università degli Studi di Parma, Viale delle Scienze, 27/A, 43124 Parma, Italy

marco.radi@unipr.it

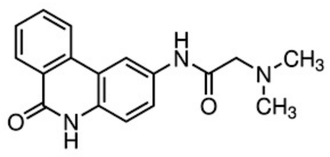
Download

Introduction

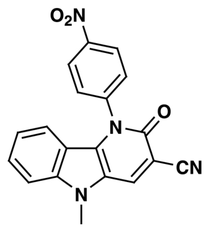
Among the nitrogen-containing hetrocycles, 2-pyridones are extensively studied scaffolds frequently found in natural and pharmaceutical compounds.
Within this family, 5,6-ring-fused derivatives present a wide range of biological activities (e.g. Huperazine A, PJ34, INDOPY-1) and can be used to study diseases such as cognitive disorders, cancer and viral infections[1-3].



Huperazine A
Acetylcholinesterase inhibitor



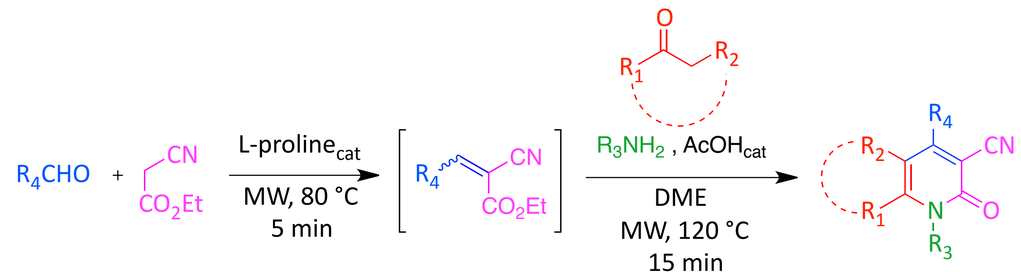
PJ34
PARP-1 inhibitor



INDOPY-1
Anti-HIV

Our optimized **one-pot two-step** protocol

In order to optimize the protocol, different solvents (DME, EtOH, *t*-BuOH, DMF), catalysts (Et_3N, piperidine, $AlCl_3$, L-proline), temperatures and reaction times were used[7]. The best results were obtained dividing the reaction in two consecutive steps, in the same reaction vessel according to the following procedure:



I step: *Knoevenagel condensation*

II step: cyclization of the in situ generated imine with the alkylidene

State of the Art

For the synthesis of highly functionalized 2-pyridones two different approaches can be employed:

Multistep:

Conversion of 4-hydroxy-6-methylpyran-2-one ino 4-hydroxy-6-methylpyridin-2-one, followed by C4 O-alkylation and N1-functionalization[4].

Limits:
- ✓ long reaction time
- ✓ expensive purifications

Multicomponent :

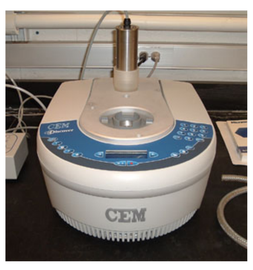
Mainly developed and investigated in recent years, allow to quickly generate functionalized 2-pyridones derivatives[5].

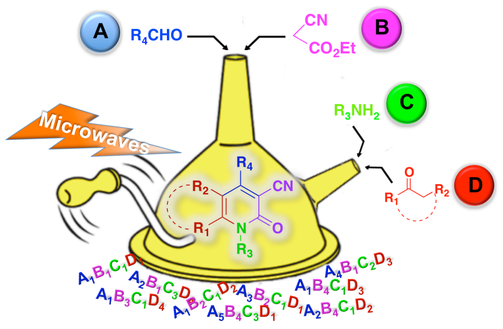
Limits:
- ✓ poor versatility
- ✓ unsuitable for ring-fused 2-pyridones
- ✓ limited to N1-unsubstituted 2-pyridones.

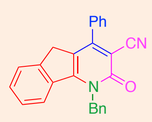
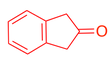
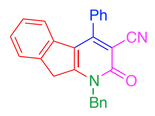
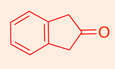
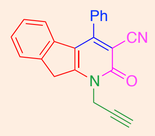
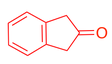
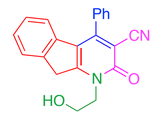
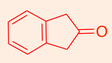
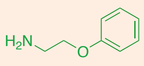
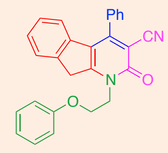
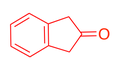
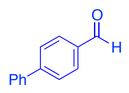
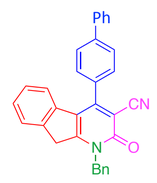
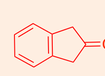
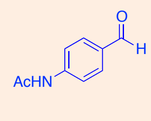
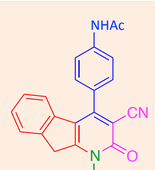
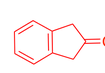
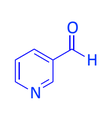
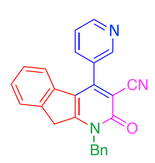
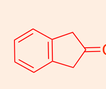
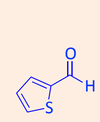
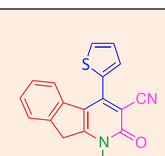
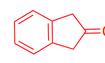
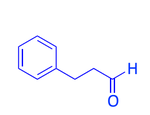
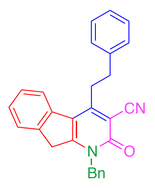
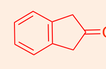
Aim of the work

Development of an efficient protocol for the synthesis of N1-substituted 5,6-ring-fused 2-pyridones:

- ✓ **versatile**, starting from commercially available aldehydes, ketones and amines
- ✓ **fast**, using the microwave irradiation
- ✓ **practical**, combining the advantages of multistep protocols (high chemical diversity) and multicomponent reactions (atom- and cost-efficiency).





Entry	Ketone	Amine	Aldehyde	Product (Yields 20-65%)
1		$BnNH_2$	PhCHO	
2		$BnNH_2$	PhCHO	
3		$BnNH_2$	PhCHO	
4		$BnNH_2$	PhCHO	
5			PhCHO	
6			PhCHO	
7			PhCHO	
8				
9		$BnNH_2$		
10		$BnNH_2$		
11		$BnNH_2$		
12		$BnNH_2$		
13		$BnNH_2$		
14		$BnNH_2$		
15		$BnNH_2$		

State of the Art

For the synthesis of highly functionalized 2-pyridones two different approaches can be employed:

Multistep:

Conversion of 4-hydroxy-6-methylpyran-2-one ino 4-hydroxy-6-methylpyridin-2-one, followed by C4 O-alkylation and N1-functionalization[4].

Limits:
- ✓ long reaction time
- ✓ expensive purifications

Multicomponent :

Mainly developed and investigated in recent years, allow to quickly generate functionalized 2-pyridones derivatives[5].

Limits:
- ✓ poor versatility
- ✓ unsuitable for ring-fused 2-pyridones
- ✓ limited to N1-unsubstituted 2-pyridones.

Aim of the work

Development of an efficient protocol for the synthesis of N1-substituted 5,6-ring-fused 2-pyridones:

- ✓ **versatile**, starting from commercially available aldehydes, ketones and amines
- ✓ **fast**, using the microwave irradiation
- ✓ **practical**, combining the advantages of multistep protocols (high chemical diversity) and multicomponent reactions (atom- and cost-efficiency).

Preliminary experiments

We were initially inspired by the multicomponent microwave-assisted synthesis of 2-amino-3-cyanopyridine published by Shi et al.[6] We have applied this protocol to cyclic ketones but the ring-fused-2-pyridone derivatives were obtained only in trace.

Compd	R_2	R_3	R_4	Yield[a] (%)
3a	Ph	H	–	80
3b			–	20
4a			H	Trace
4b			Bn	–

[a] Isolated yield.

Conclusions and future perspectives

A practical one-pot, two-step microwave-assisted protocol for the direct synthesis of N1-substituted 5,6-ring-fused 2-pyridones has been developed.

This method proved to be effective on a series of aldehydes, ketones and amines and could be profitably exploited in drug-discovery settings for the rapid identification of biologically relevant hit compounds.

References

1) Kozikowski, A. P. et al. *Acc. Chem. Res.* **1999**, *32*, 641–650; 2) Jagtap, P. et al. *Crit. Care Med.* **2002**, *30*, 1071–1082; 3) Jochmans, D. et al. *Antimicrob. Agents Chemother.* **2006**, *50*, 2772-2781; 4) Selness, S. R. et al. *Bioorg. Med. Chem.* **2011**, *21*, 4059-4065; 5) (a) Pathak, S. et al. *Tetrahedron Lett.* **2012**, *53*, 3030-3034; (b) Gorobets,N. Y. et al. *Tetrahedron* **2004***, 60,* 8633-8644; (c) Serry, A. M. et al. *J. Comb. Chem*. **2010**, *12*, 559-565; 6) Shi, F. et al. *ARKIVOC* **2005**, *i*, 137-142; 7) Radi M. et al. *Tetrahedron Lett*. **2013**, *54*, 6905-6908.