MICROWAVE-ASSISTED MULTICOMPONENT SYNTHESIS OF RING-FUSED 2-PYRIDONES

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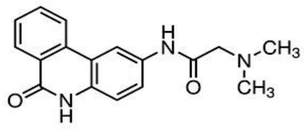
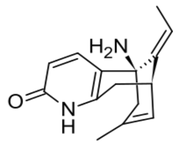
Background

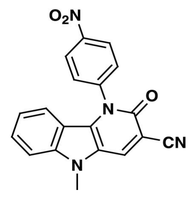
2-Pyridones are a class of extensively investigated heterocycles widely distributed in nature and endowed with interesting biological activities. Ring-fused-2-pyridones are currently used in the treatment of proliferative diseases (Topotecan) and are also reported as acetylcholinesterase inhibitors (Huperzine A), PARP-1 inhibitors (PJ34), antibacterial agent (ABT-719) and anti HIV-agent (INDOPY-1). Thus can be considered as versatile chemical probes to study different diseases[1-3].



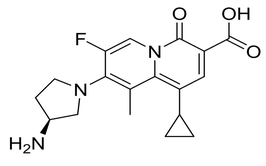
PJ34
PARP-1 inhibitor



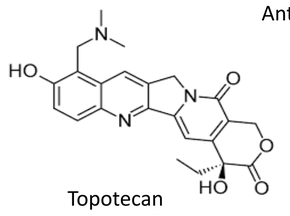
Huperazine A
Acetylcholinesterase inhibitor



INDOPY-1
Anti-HIV



ABT-719
Bacterial Topoisomerase I inhibitor



Topotecan
(*Hycamtin™*)
Human Topoisomerase inhibitor

State of the Art

Two approaches for 2-Pyridones synthesis:

- **MULTISTEP**
  1) Conversion of 4-OH-2-pyrone to 4-OH-2-pyridone
  2) O-alkylation in C4 and N1-alkylation
  3) Further steps to functionalize C3 and C5 positions[4]
- **MULTICOMPONENT**
  - ✓ Atom- and Cost-Efficiency
  - ✓ Rapid generation of 2-pyridone core[5]

Drawbacks

- ✕ Long reaction times
- ✕ Numerous purifications
- ✕ Unsuitable for ring-fused 2-pyridones
- ✕ Poor versatility

Aim of the Work

Develpoment of a microwave-assisted one-pot procedure for the direct synthesis of N1-substituted and N1-unsubstituted 5,6-ring fused 2-pyridones:

- ✓ **Quick** thanks to microwave irradiation
- ✓ **Practical** starting from commercially available amines, aldehydes and ketones
- ✓ **Versatile** Atom- and Cost-Efficient protocol, suitable for generation of high degree of chemical diversity

Our Methodology

Starting from the work of Shi et al[6] we optimized different parameters:

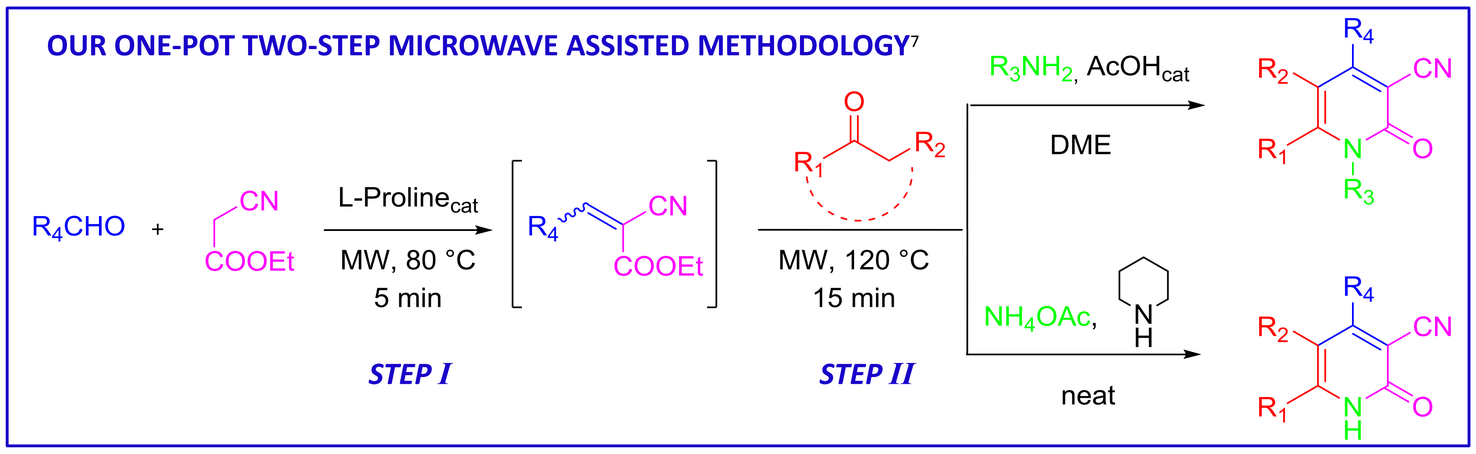
- Solvents (EtOH, *t*-BuOH, DMF, DME)
- Catalyst (piperidine, $AlCl_3$, NEt_3, L-proline)
- Temperature
- Reaction times

We obtained the best results (Yields:20-65 %) by dividing the reaction in two consecutive steps in the same reaction vessel:

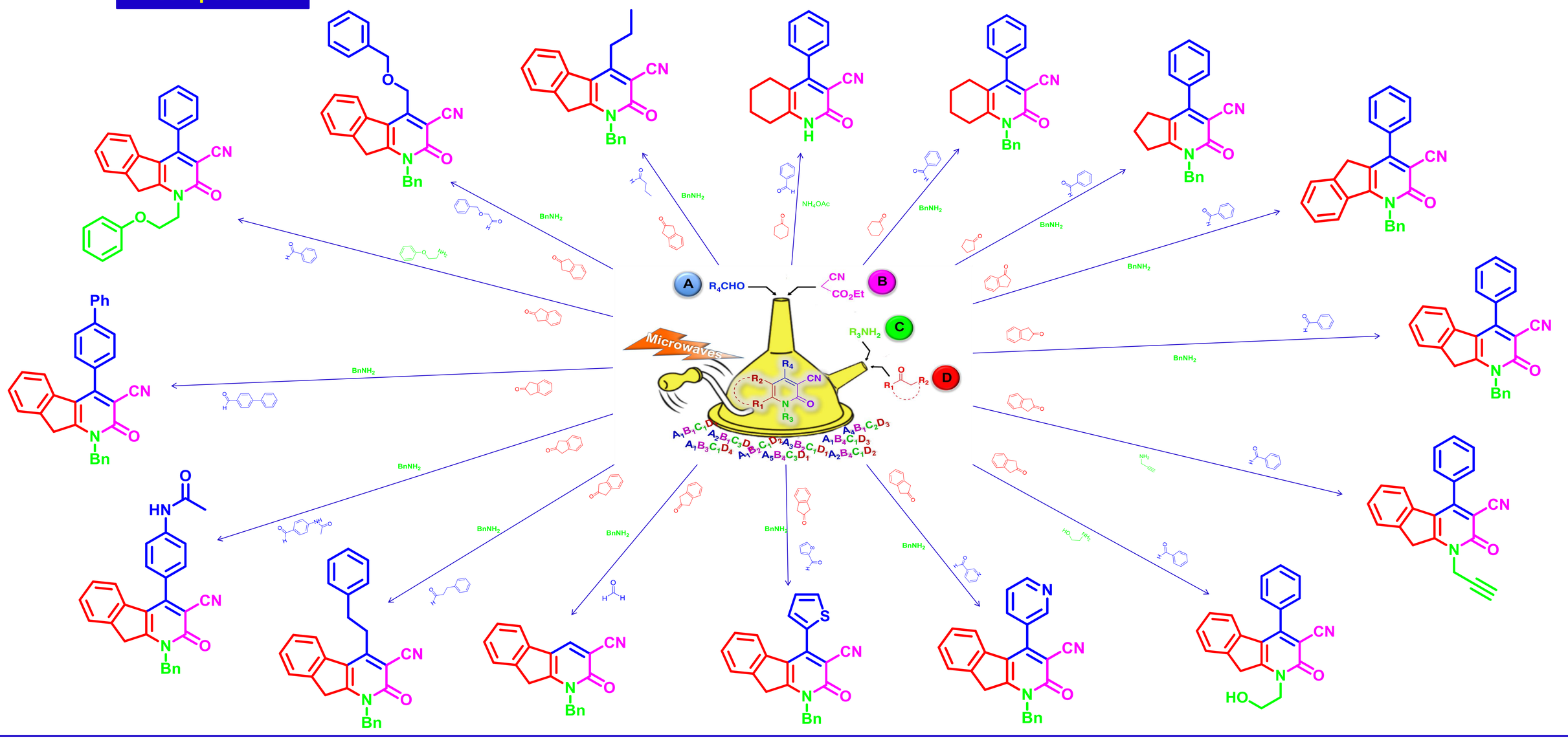
I. **Knoevenagel reaction**

II. **Cyclization** with the *in-situ* formed imine

OUR ONE-POT TWO-STEP MICROWAVE ASSISTED METHODOLOGY[7]



Compounds



Conclusion

A fast and versatile microwave-assisted one-pot two-step protocol for the synthesis of N1-substituted and N1-unsubstituted 5,6-ring-fused 2-pyridone has been developed.
This protocol could be exploited in drug-discovery campaign to generate a high degree of chemical diversity, leading to the rapid identification of biologically relevant hit compounds.

References

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