Efficient TBD-Catalyzed Synthesis of Capsaicin-like Molecules

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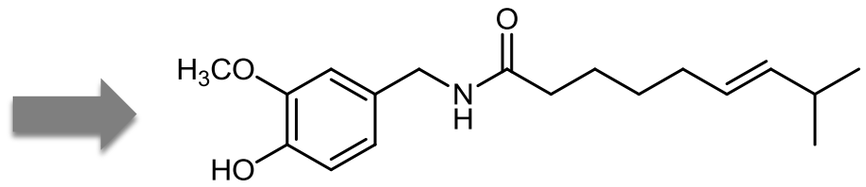
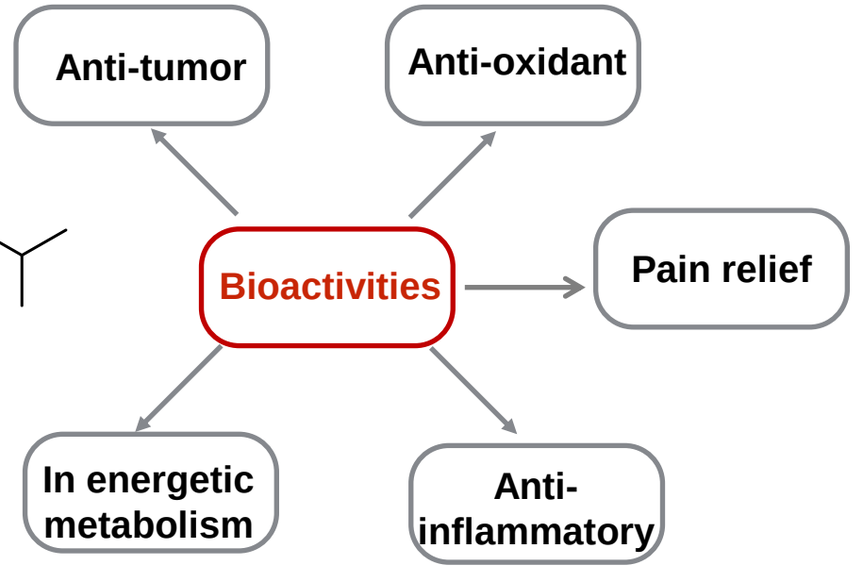
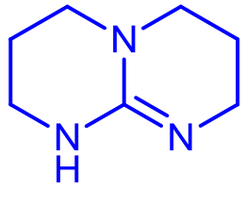
- **Capsaicin** is the natural molecule responsible for the spicy flavor of peppers, known for its biological activities.





- The length of alkyl chain affects piquancy, with the possibility of obtaining **non-pungent** synthetic capsaicin **analogues** preserving interesting bioactivities.[1]

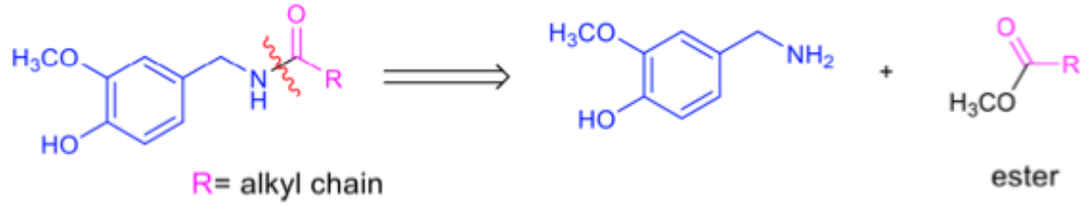
- This is the first **TBD-catalyzed microwave-assisted** aminolysis of esters[2] applied to the synthesis of capsacinoids.



1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)

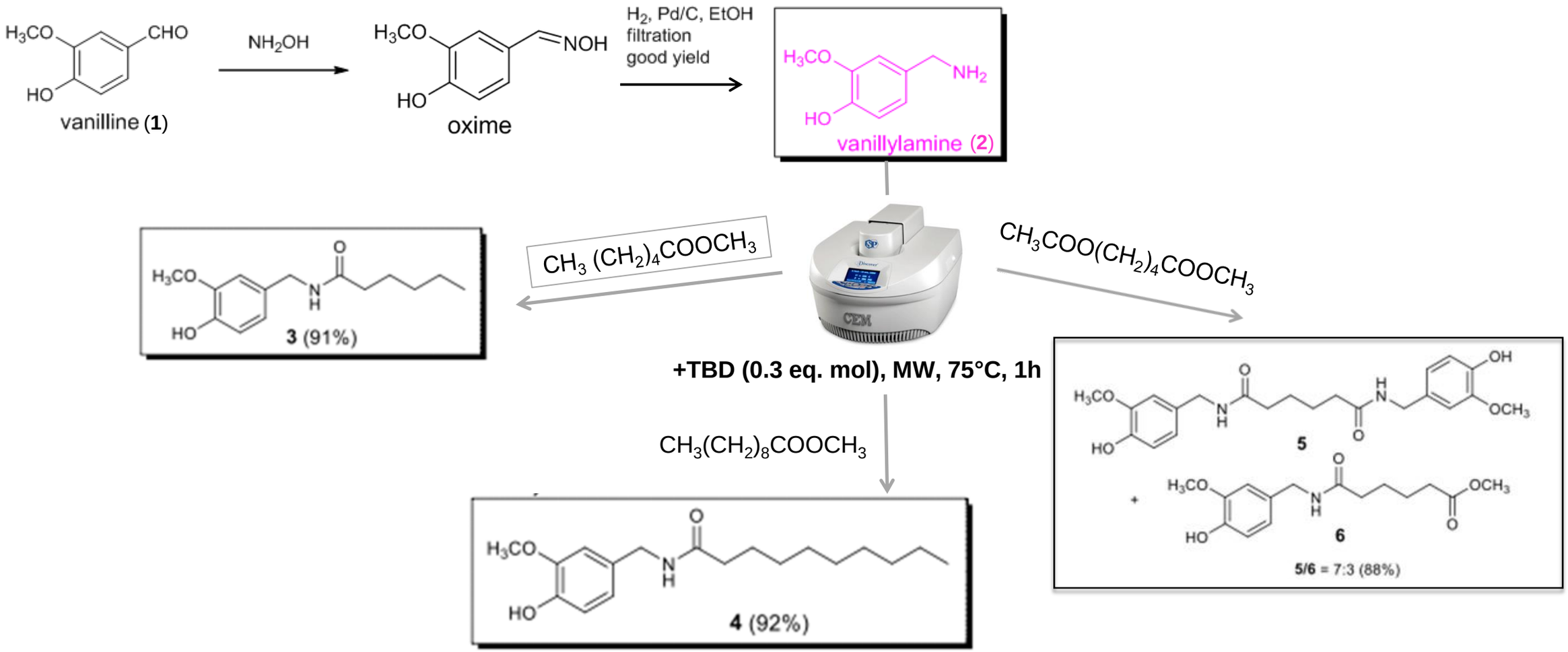
- It is a non-toxic and inexpensive catalyst, with an easy recovery.

Retrosynthetic Analysis



- without need of protecting –OH group
- MW-irradiation (reduced reaction time, high yields)
- Under solvent-free conditions

Scheme: Synthesis of Capsacinoids 3-6



- Each reaction was carried out in a sealed tube under MW-irradiation by a *CEM Discover* reactor, monitoring the temperature by an infrared control system.
- Each reaction yield was calculated on the chromatographically purified products.
- Products were structurally characterized by NMR (400 MHz, $CDCl_3$) and ESI(-)-MS/MS analysis.

Conclusions

- Capsaicin analogues, different in alkyl chain moiety, were first obtained by a TBD-catalyzed aminolysis of esters.
- MW irradiation and solvent-free conditions allowed an efficient and eco-friendly procedure.
- The recovery of TBD catalyst and its reuse have proven to be effective.
- This synthesis represents a valid alternative to both the known chemical procedure (using sensitive acyl chlorides and protection/deprotection of the phenol group) and lipase-catalyzed system (requiring controlled conditions of pH, temperature and solvent), used so far to synthesize capsacin-like molecules.

Perspectives

- The method here reported can be successfully exploited for the access to wide libraries of capsaicinoids for further biological evaluations, as well as for a large-scale production.

References

[1] M.L.Reyes-Escogido, E. G.Gonzalez-Mondragon, E.Vazquez-Tzompantzi, *Molecule*s **2011**,*16*,1253.
[2] C. Sabot, K. A. Kumar, S. Meunier, C. Mioskowski, *Tetrahedron Lett*. **2007**,*48*,3863.