Late-stage oxygenation towards the preparation of metabolites of agrochemical active ingredients

Duarte B. Clemente[a,b]*, Carlos M. Monteiro[c], Jaime A. S. Coelho[a]

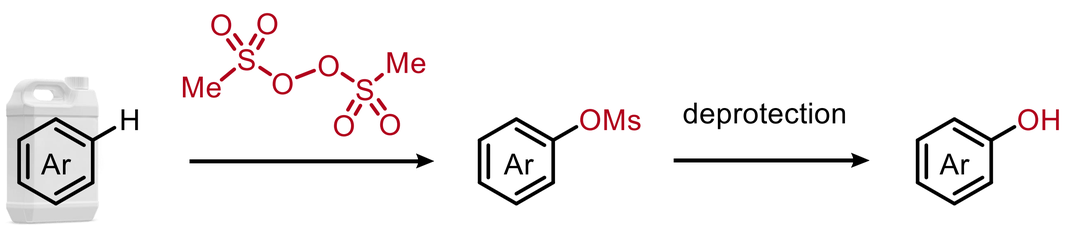
[a]Centro de Química Estrutural, Institute of Molecular Sciences, Faculty of Sciences, University of Lisbon, Campo Grande, 1749-016, Lisbon, Portugal.
[b]Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Campo Grande, 1749-016, Lisbon, Portugal.
[c]ASCENZA Agro, S.A., Screening and Synthesis Laboratory, Setúbal, Portugal.
***Email: duarteclemente@alunos.fc.ul.pt**

Motivation

The development of plant protection products requires the safety profile analysis of active ingredients (AI), which includes synthesis and (eco)toxicity determination of **metabolites**. C-oxygenation is a very common phase-I metabolism reaction, catalyzed by cytochrome P450 enzymes[1,2]. Thus, the synthesis of **oxygenated AI metabolites** is of great importance for agrochemical producing companies, such as ASCENZA Agro[3].

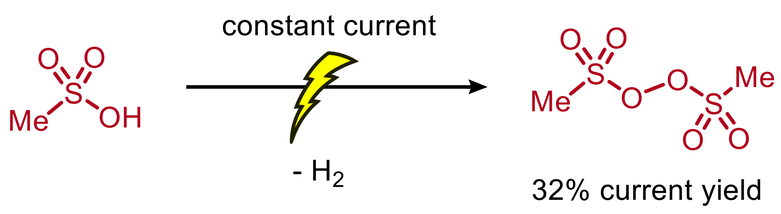
AI hydroxylation strategy

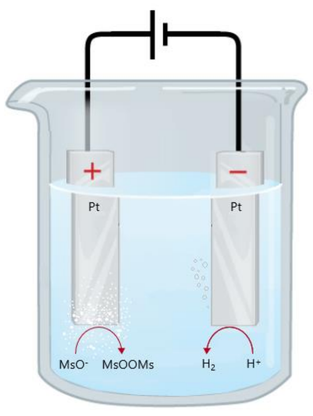
Synthesis of hydroxylated aromatic metabolites of several active ingredients, using a method described by Tobias Ritter and co-workers[4]. This method allows for the **late-stage** oxygenation of the aromatic positions, by generating mesylate derivatives with bis(methanesulfonyl) peroxide as an oxidant, followed by conversion to the corresponding phenols.



Synthesis of MsOOMs

MsOOMs is a sulfonyl peroxide known since 1951[5], and can be prepared by anodic oxidation of methanesulfonic acid, by **electrolysis** of an aqueous MsOH solution at constant current, in an undivided electrochemical cell[6].





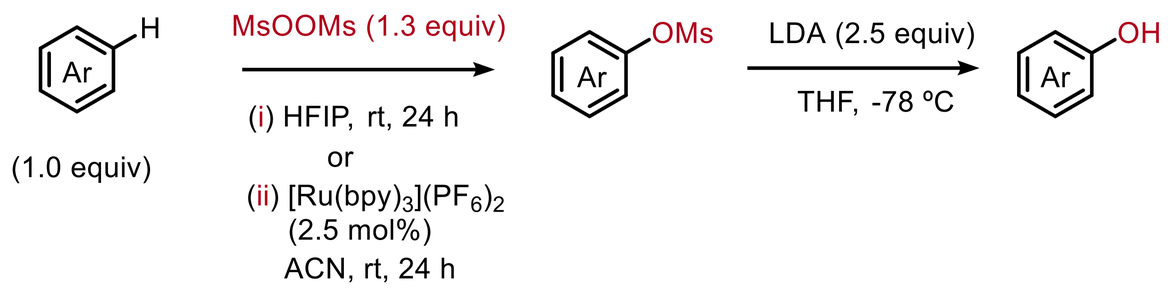
Optimized electrolysis conditions:

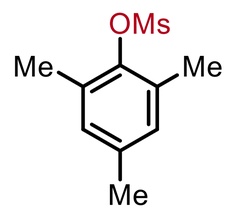
- [MsOH] = 10 M
- Pt electrodes
- I = 1.0 A
- t = 2 h
- V = 50 mL
- T = 20 ºC

Since MsOOMs is insoluble in water, performing the electrolysis of an aqueous MsOH solution allows the **re-electrolysis of the solution**, by adding new MsOH after filtering off the peroxide.

Stable at room temperature, **decomposes explosively** at temperatures greater than 50 ºC.

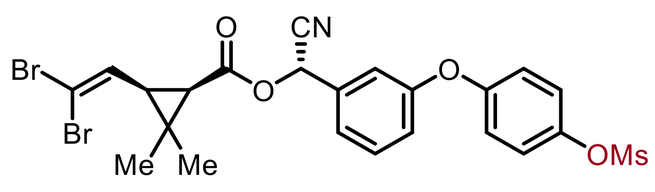
Aromatic oxygenated derivatives of AIs





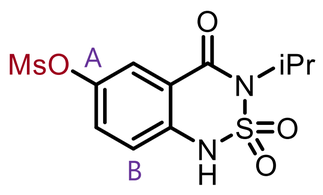
from mesitylene

64%[i]



from deltamethrin

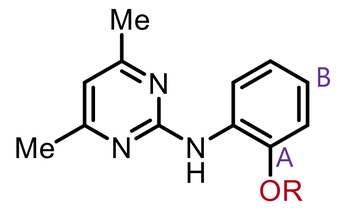
30%[i]



from bentazone

A:B
1:0.6

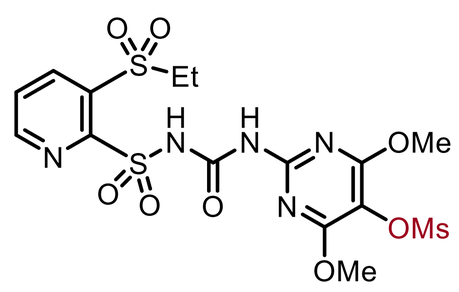
13%[i]



from pyrimethanil

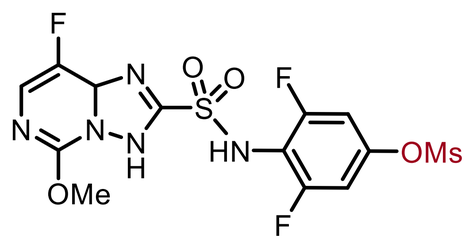
A:B
1:1

R = Ms 47%[i]
R = H 71%



from rimsulfuron

no reaction[i,ii]



from florasulam

traces[i,ii]

Conclusions

The synthesis of several mesylate derivatives of agrochemical AIs was achieved, with good to satisfactory results, using a previously described method. The conversion of the pyrimethanil mesylate derivatives to the corresponding hydroxylated metabolites was accomplished with good results. Additionally, the optimization of a method for the synthesis of the peroxide reagent was attained.

References

[1] Reichl, F.-X.; Schwenk, M. *Regulatory Toxicology*, 2nd ed.; Reichl, F.-X., Schwenk, M., Eds.; Springer Nature Switzerland AG: Cham, Switzerland, **2021**. [2] *Chem. Res. Toxicol.* **2001**, *14* (6), 611–650. [3] https://www.ascenza.pt/. [4] *J. Am. Chem. Soc.* **2018**, 140 (47), 16026–16031. [5] U.S. Patent 2619507A, Nov 25, 1952. [6] *J. Chem. Soc.* **1964**, 4901–4907.

Acknowledgements

Financial support from Fundação para a Ciência e a Tecnologia (FCT, UIDB/00100/2020, UIDP/00100/2020, LA/P/0056/2020 and 2020/02383/CEECIND). The authors thank Dr. Ana Viana and Dr. Jorge Correia (CQE-FCUL) for assistance and equipment to perform electrolysis.