Development of a low environmental impact couple of solvent and catalyst for Nenitzescu reaction

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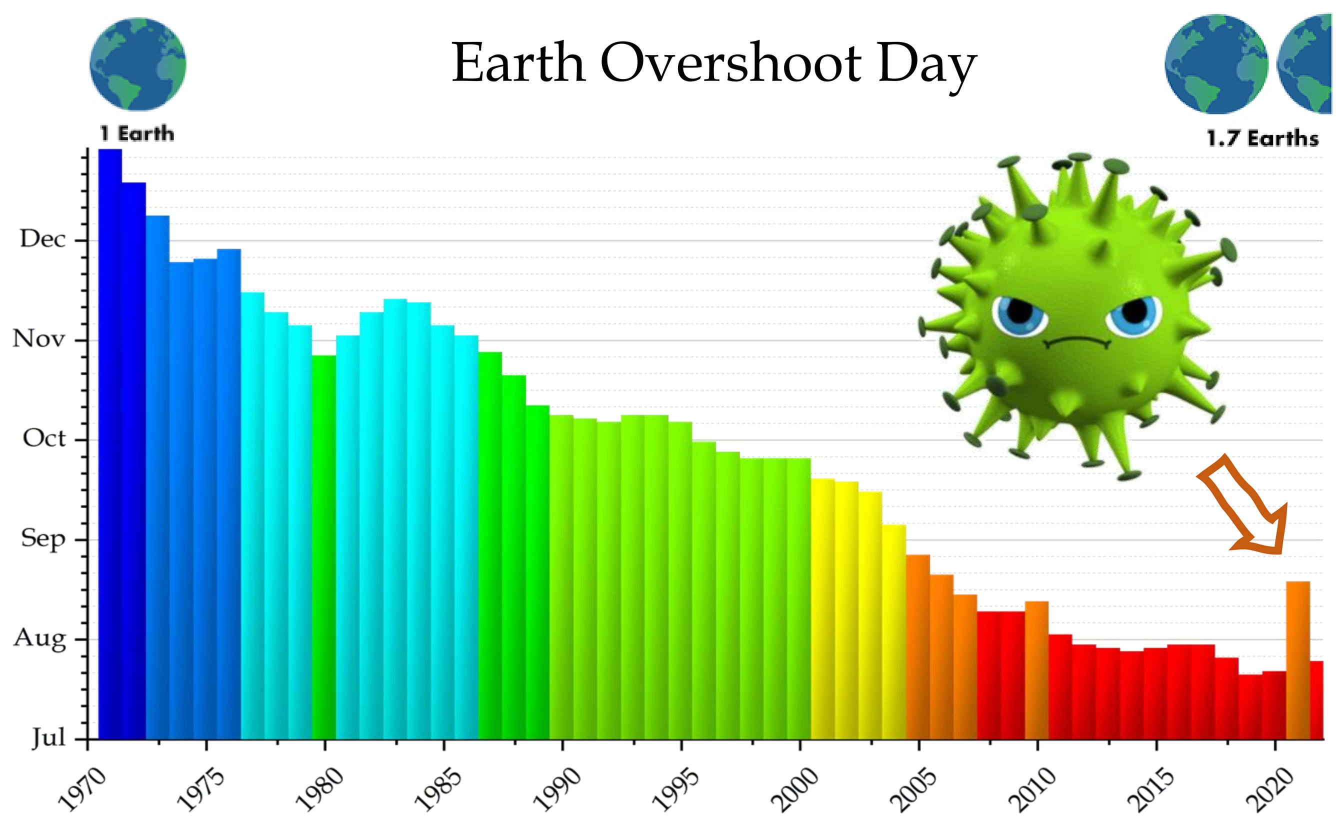
Abstract

Indole is an important core in many biogenic compounds such as tryptophan, serotonin, melatonin and many other hormones, alkaloids and secondary metabolites. The reaction discovered by *Costin Nenitzescu* in 1929[1] is attractive when a 5-hydroxyindole is needed, because the reactants are enamines and quinones, cheap and simple starting materials. Major advancements in this reaction have been done by the group of *Velezheva*[2], that developed the application of mild Lewis acids, such as zinc chloride, to perform the reaction in **dichloromethane**. In the context of reduction of environmental impact, we aimed to substitute dichloromethane and zinc with less toxic and polluting solvents and catalysts to find that **cyclopentyl methyl ether (CPME)** is an effective solvent for this synthesis at room temperature and **magnesium** salts can provide yields comparable to **zinc** for a few substrates.

Why we do care?

Nowadays it is well known that year by year we are overwhelming the earth biocapacity faster and faster. It's sad to see that we needed a pandemic to move forward the *Earth Overshot Day* in 2020. Chemistry can help the environmental preservation by optimizing synthetic processes.

Many parameters have been proposed to monitoring the greenness of a chemical processes. Two of them are *Environmental Factor* and *Process Mass Intensity* (PMI). The E-Factor is the ratio of the mass of waste per mass of product. PMI calculates the ratio of the total mass of materials to the mass of the isolated product. A relevant factor is the nature of the solvent (petroleum or renewable product), and its recyclability.

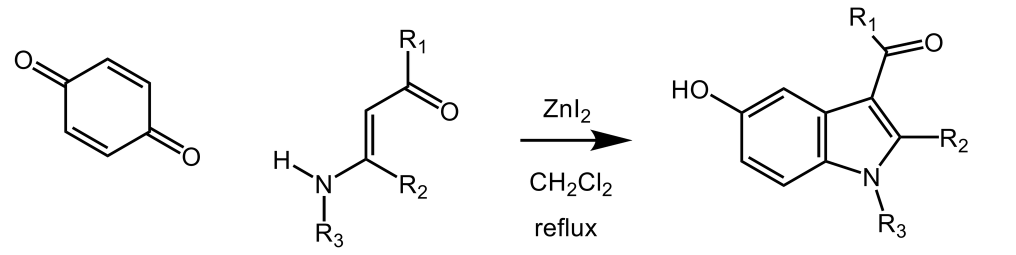


$$E\ Factor = \frac{Total\ Waste\ Mass}{Mass\ of\ Product}$$

$$Process\ Mass\ Intensity = \frac{Total\ Mass\ of\ Materials}{Mass\ of\ Isolated\ Product}$$

Previous works

Velezheva et al. (2006)



R_1 = OEt, Me, NHPh
R_2 = Me, Et, Ph, $(CH_2)_5$
R_3 = H, Me, Ph, CH_2Ph, $(CH_2)_5$, 4-Br-Ph

Reflux ➜ energy consumption

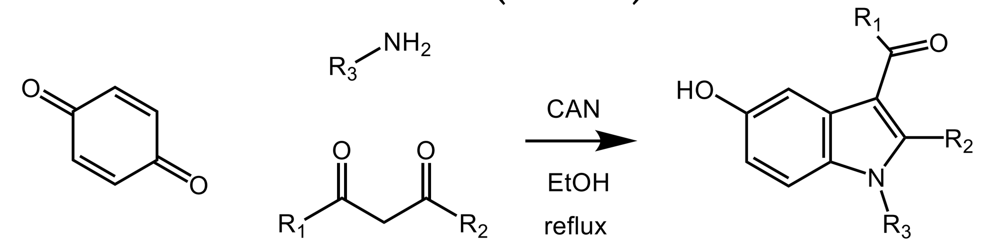
Use of chlorinated solvent

Enamine synthesis is needed

E Factor ~10

PMI ~30

Menéndez et al. (2010)

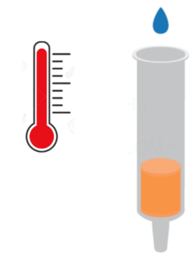


R_1 = OEt, S-'Bu
R_2 = Me, n-Pr
R_3 = Bu, Allyl, Bn, Propalgyl

Reflux ➜ energy consumption

Expensive catalyst

Large use of solvents in purification by chromatographic column



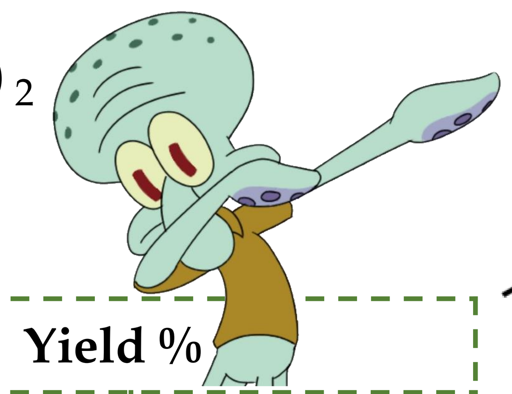
E Factor ~40

PMI ~170

Results

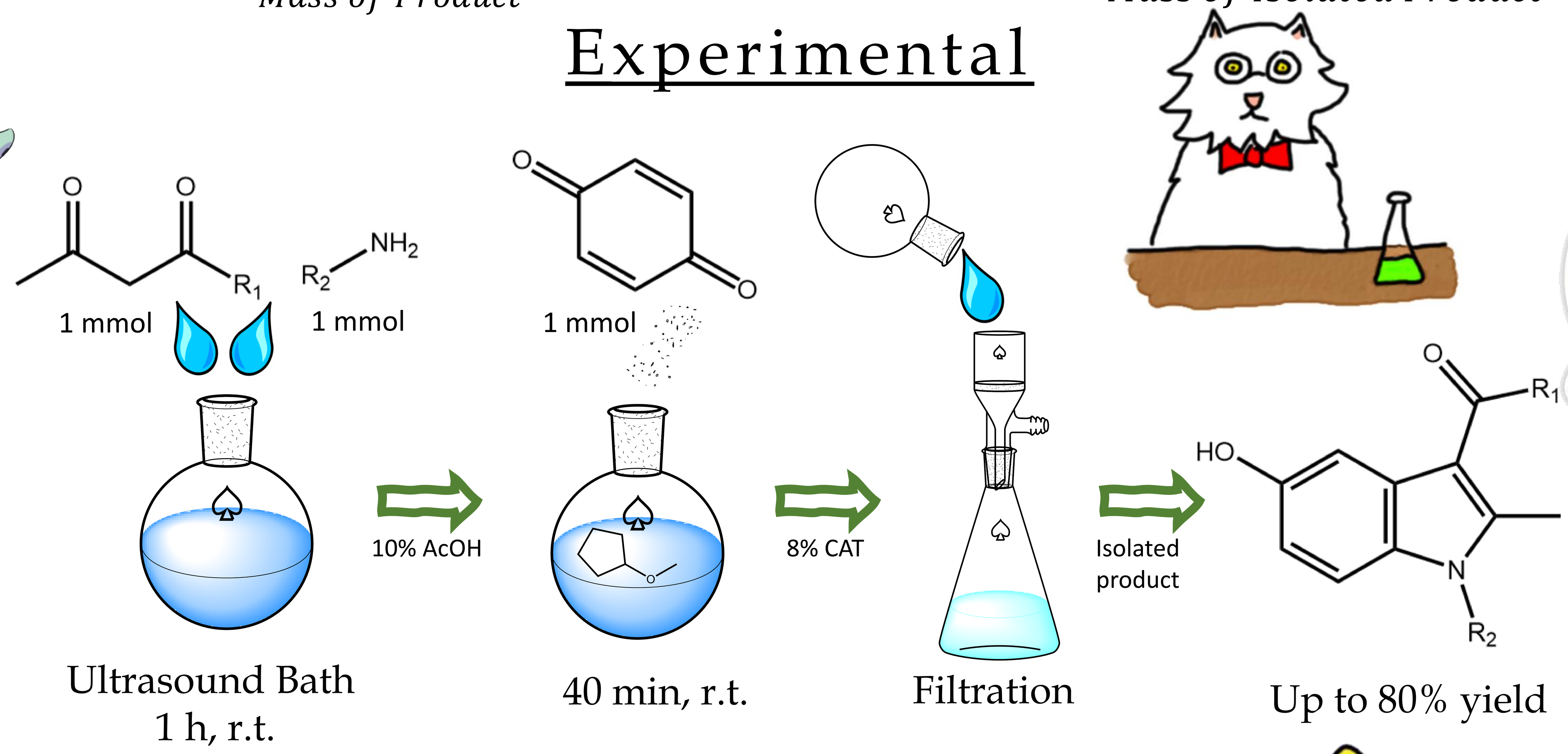
Catalysts: ZnI_2 / $ZnCl_2$ / $Mg(CF_3SO_3^-)_2$

Solvent: CPME



R1	R2	Yield %		
		$ZnCl_2$	ZnI_2	$Mg(CF_3SO_3^-)_2$
Acetyl	4-Cl-Benzyl	74	80	10
Acetyl	4-F-Benzyl	70	60	27
Ethyl ester	Hydroxyethyl	54	54	51
Ethyl ester	Benzyl	55	61	36
Acetyl	n-pentyl	49	55	34
Acetyl	Benzyl	38	47	25
Ethyl ester	4-Cl-Benzyl	50	51	38
Acetyl	Benzyl	38	47	25
Ethyl ester	n-pentyl	22	35	17
Acetyl	Hydroxyethyl	10	21	trace

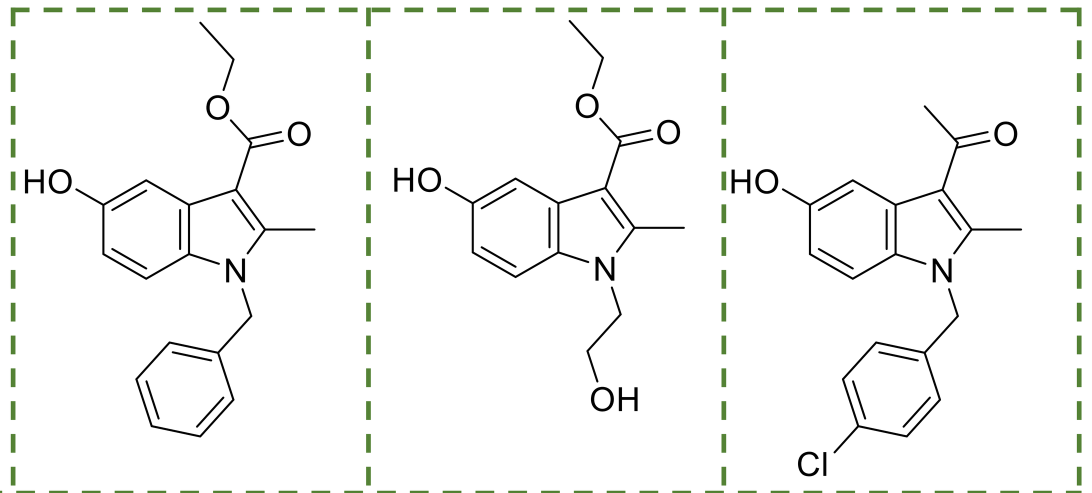
Experimental



Conclusions

- ❑ Synthesis of a library of substituted indoles
- ❑ Fast and room temperature
- ❑ Straight forward work-up
- ❑ Waste reduction (solvent recycle)

Green Metrics



Literature Yield %	73[3]	83[2]	-
This Work Yield %	61	54	80
Literature E Factor	40	10	-
This Work E Factor	5	4	2

1. C. D. Nenitzescu, Bull. Soc. Chim Romania, 11, 1929, 37–43.
2. V. S. Velezheva, A. G. Kornienko, S. V. Topilin, A. D. Turashev, A. S. Peregudov, P. J. Brennan, J. Heterocyclic Chem. 43, 2006, 873–879
3. Suryavanshi PA, Sridharan V, Menéndez JC. Org Biomol Chem. 2010;8(15):3426–36.