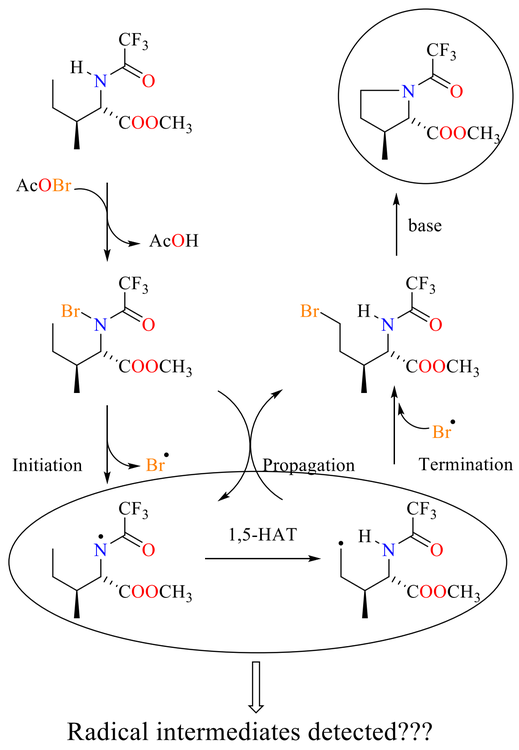
EPR and NMR Investigation of Hofmann–Löffler–Freytag Reaction: Detection of *N*-centered Radical

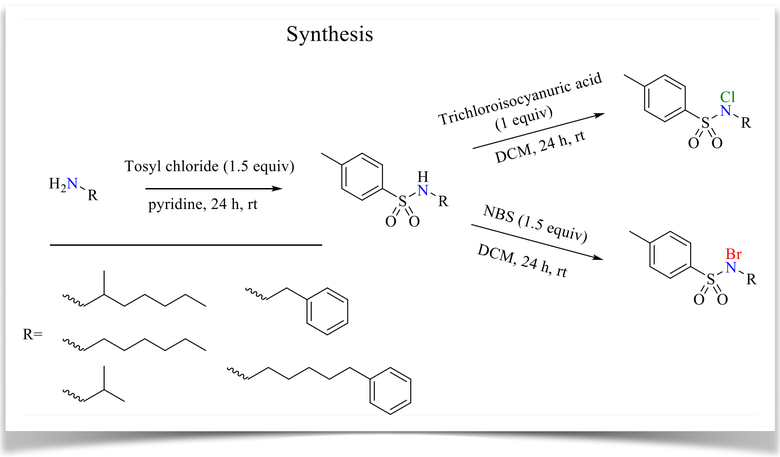
Gabrijel Zubčić,[a] Jiangyang You,[b] Maria Kolympadi Marković,[c] Fabian Zott,[d] Salavat Ashirbaev,[d] Erim Bešić,[a] Valerije Vrček,[a] Hendrik Zipse,[d] and Davor Šakić[a]

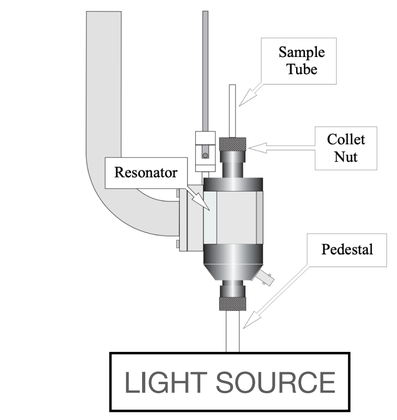
[a] University of Zagreb, Zagreb, Croatia [b] Institute Ruđer Bošković, Zagreb, Croatia [c] University of Rijeka, Rijeka, Croatia [d] Ludwig-Maximilians-Universität München, München, Germany

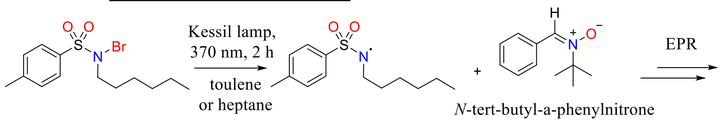
- The Hofmann-Löffler-Freytag (HLF) reaction is used to functionalize distant C-H bonds,[1] producing pyrrolidine rings or C5-substituted compounds.
- Crucial step of the reaction mechanism involves a rearrangement from an *N*-centered radical via 1,5-hydrogen atom transfer (HAT).
- Although, Roizen[2] and Muñiz[3] groups have reported on the formation of piperidine and C6-halogenated products via 1,6-HAT.

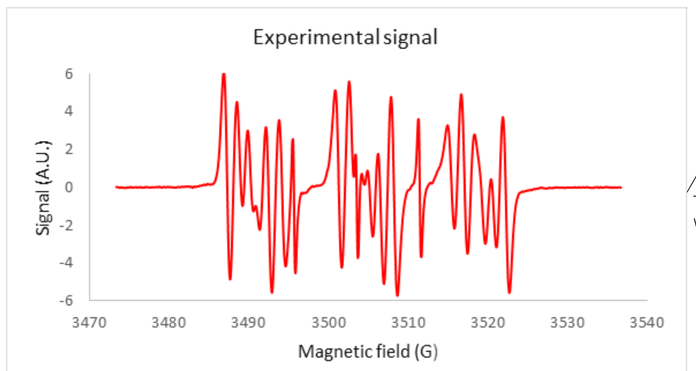


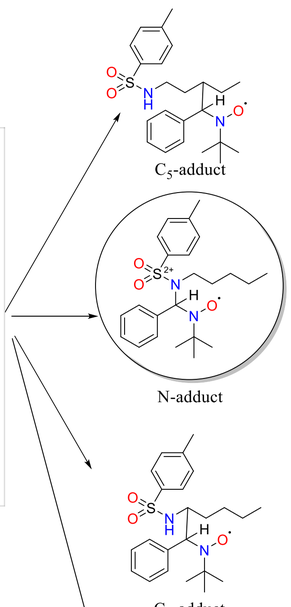
- The Muñiz group[4] claims to have detected *N*-centered radicals using EPR measurements. This would be the first finding of radical intermediates in the HLF reaction.
- However, Khort[5] has disproved work done by the Muñiz group with his theoretical calculations.



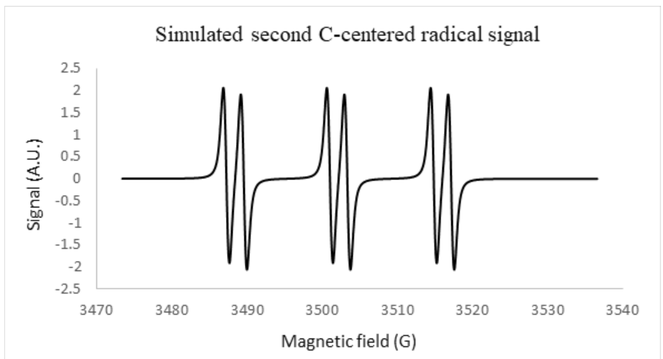






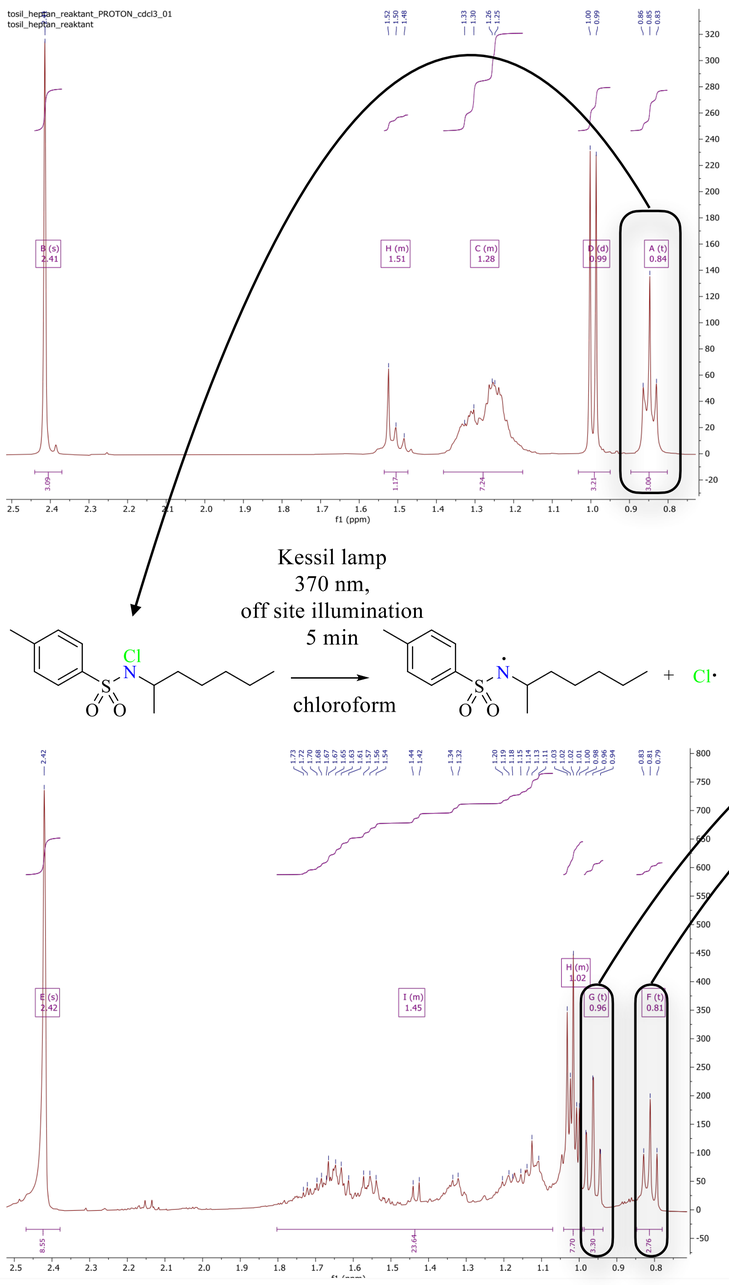


Desomposition and simulation in Mathematica

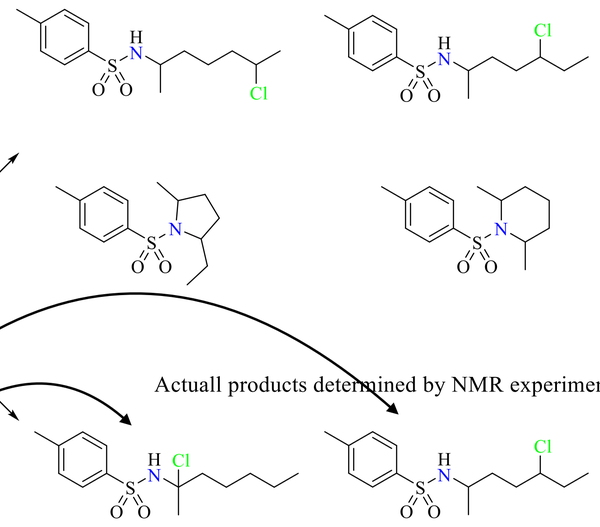


Matherials and methods

- Thin-layer chromatography-TLC
  - Thin-layer chromatography was performed on pre-coated TLC plates ALUGRAM SIL G/UV254, 0.20 mm silica gel 60 with fluorescent indicator UV254 (Macherey-Nagel) in the appropriate solvent system. TLC spots were observed after illumination with UV light at a wavelength of 254 nm.
- Column chromatography
  - Chromatographic purification of the products was carried out by chromatography on columns filled with silica gel (Macherey-Nagel) 0.063-0.2 mm, and appropriate solvent mixtures were used as eluents: petroleum ether/ethyl acetate,
- Electronic paramagnetic resonance
  - ELEXSYS E 500 EPR X-band spectrometer (Electron paramagnetic spectrometer)
  - Spin trap, PBN, N-tert-butyl-α-phenylnitrone
- Nuclear magentic resonance
  - Varian Inova 400 NMR spectrometer.
  - Probe: Varian OneNMR Probe, 1H-19F/ 15N-31P Z PFG for direct and indirect detection (-80 to 130°C)



Expected products according to the literature



Actuall products determined by NMR experiments

Conclusions

- 1,5- and 1,6-HAT processes are elementary steps of the HLF reaction mechanism
- Regioselectivity of the reaction is affected by a reverse 1,5-HAT process.
- Preliminary *N*-centered radical with PBN trap -^{15}N labeled experiments for final conclusion
- Essential elementary step of the HLF reaction is intramolecular
- Whole reaction was observed in NMR experiments.

References

[1]. T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.*, **2016**, *45*, 546.
[2] M. A. Short, M. F. Shehata, M. A. Sanders, J. L. Roizen, *Chem. Sci.*, **2020**, *11*, 217.
[3] H. Zhang, K. Muñiz, *ACS Catal.*, **2017**, *7*, 4122.
[4] A. E. Bosnidou, T. Duhamel, K. Muñiz, *Eur. J. Org. Chem.*, **2020**, *40*, 6361
[5] H. Korth, *Eur. J. Org. Chem*., **2020**, *40*, 6366.

HRZZ Croatian Science Foundation

LIGHT-RING

HRZZ project UIP 2020-02-4857