Detecting elusive radicals using spin traps. Case study on Hofmann-Löffler-Freytag reaction

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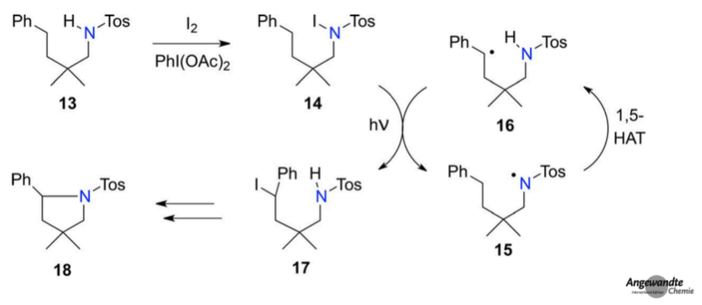
HRZZ Croatian Science Foundation

SYNTHESIS OF 1,4-EPIMINE COMPOUNDS. IODOSOBENZENE DIACETATE, AN EFFICIENT REAGENT FOR NEUTRAL NITROGEN RADICAL GENERATION
Tetrahedron Letters,Vol.26,No.20,pp 2493-2496,1985
P. de Armas, R. Carrau, J.I. Concepción, C.G. Francisco, R. Hernández, and E. Suárez

Suárez



Muñiz

Angewandte International Edition

Synthetic Methods

An Iodine-Catalyzed Hofmann–Löffler Reaction**

*Claudio Martínez and Kilian Muñiz**

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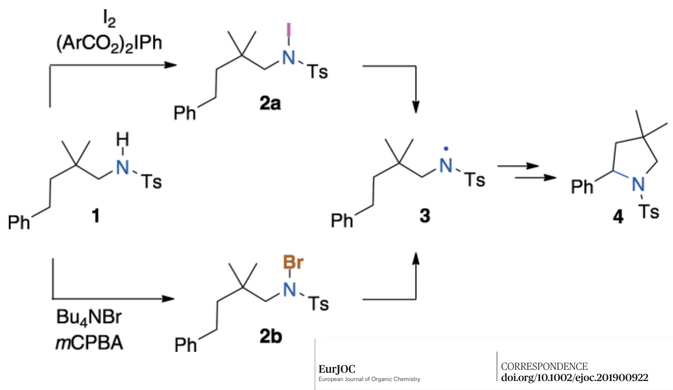
Communication

Amidyl Radical Intermediates | *Very Important Paper* |

Detection of the Elusive Nitrogen-Centered Radicals from Catalytic Hofmann–Löffler Reactions

Alexandra E. Bosnidou,[a,b] Thomas Duhamel,[a,c] and Kilian Muñiz*[a,d]



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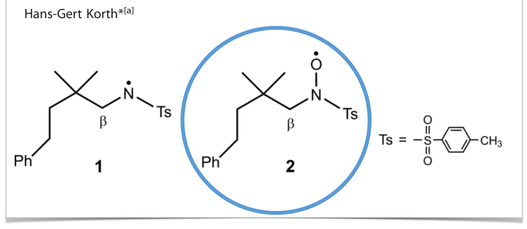
Amidyl Radical Intermediates

Comment on "Detection of the Elusive Nitrogen-Centered Radicals from Catalytic Hofmann–Löffler Reactions"

Hans-Gert Korth*[a]

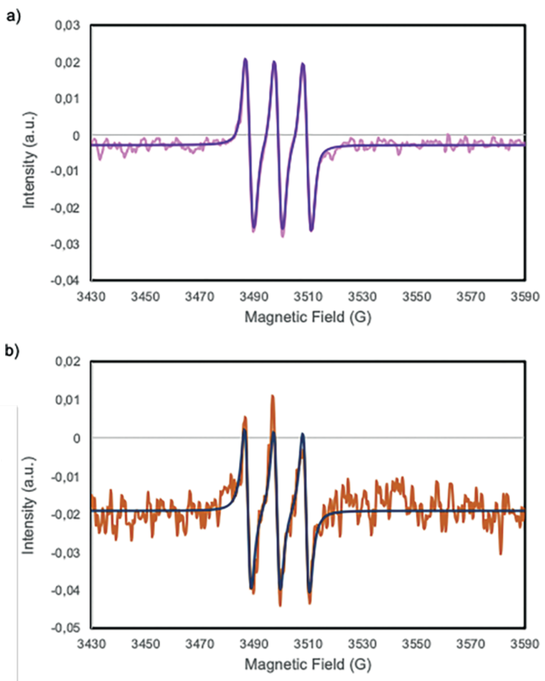


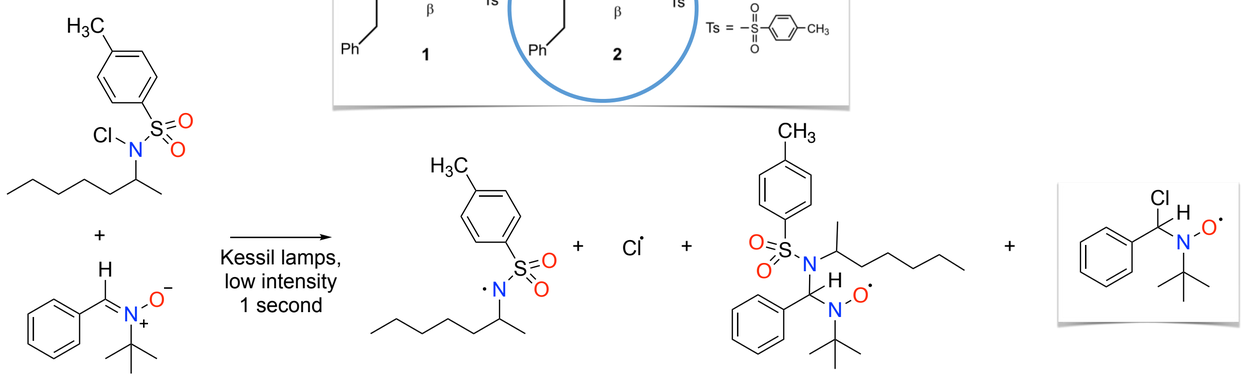
Hofmann-Löffler-Freytag reaction

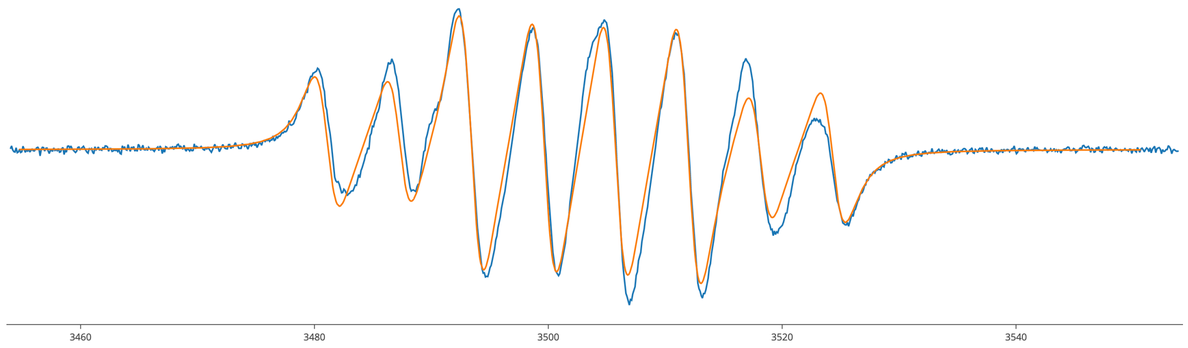
- The Hofmann-Löffler-Freytag (HLF) reaction was discovered in the late 19th and has advanced rapidly in the last 20 years
- It is used to form a C-N bond at unsubstituted C-H positions, as well as to insert pyrrolidine and piperidine rings in an environmentally friendly manner, without the use of expensive metal catalysts and through highly efficient syntheses
- Mechanism of this reaction is not yet clearly understood, and further experiments are needed to determine all reaction parameters

Electron paramagnetic resonance and HLF

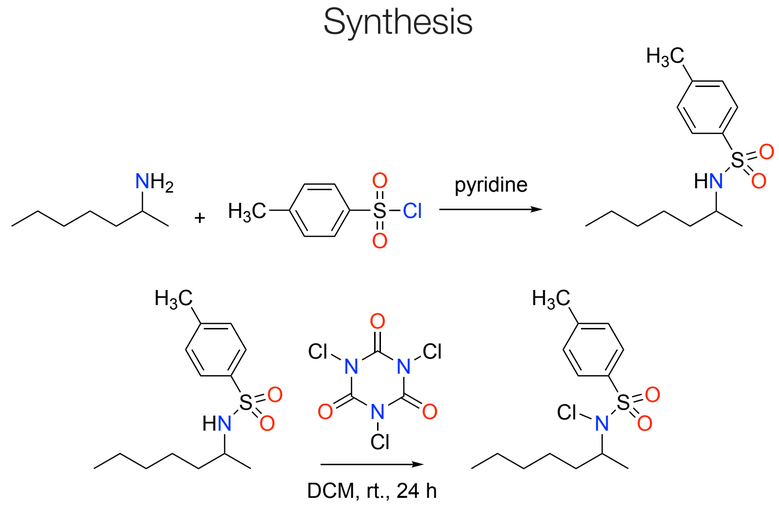
- *N*-centered radical has supposedly been detected via EPR measurements by the Muñiz group.[1] This would represent the first detection of radical intermediates in the HLF reaction
- However, suspicion was raised by Khort,[2] who has disproved work done by the Muñiz group with his calculations

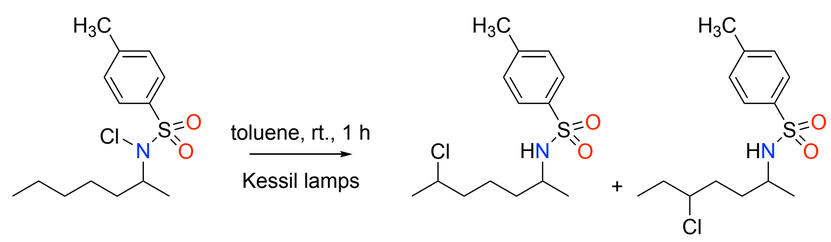






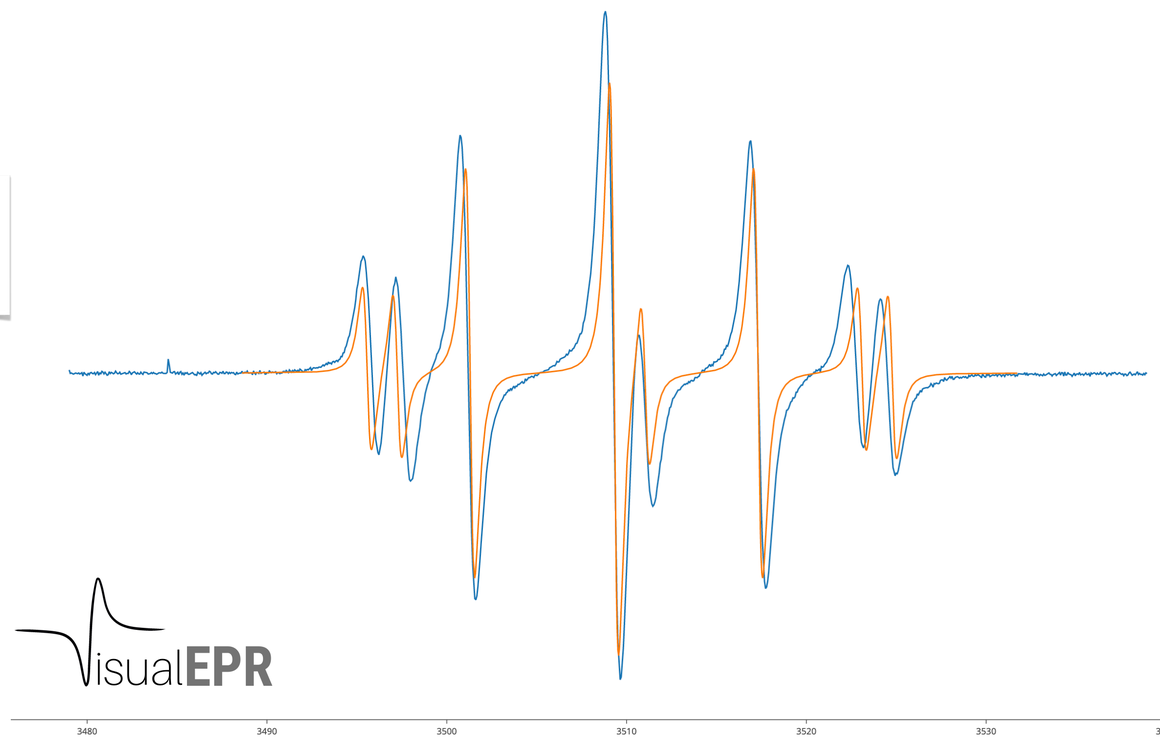
Synthesis



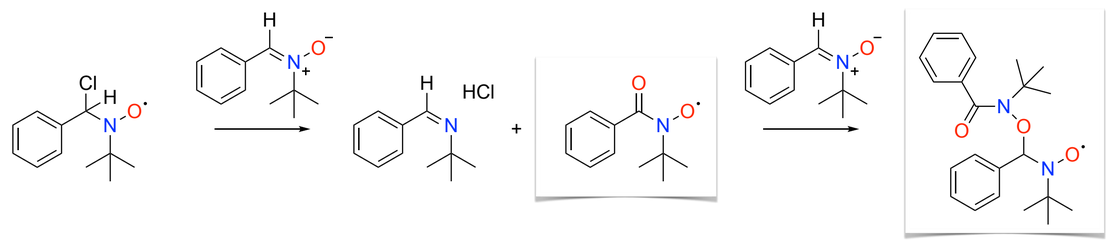


Materials and methods

- Thin-layer chromatography-TLC 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, with UV detection at 254 nm after immersion in an aqueous solution of $KMnO_4$ followed by heating
- Column chromatography on silica gel (Macherey-Nagel) 0.063-0.2 mm, and appropriate solvent mixtures were used as eluents: petroleum ether/ethyl acetate
- FTIR spectra recorded on an Agilent Cary 630 FTIR spectrometer with air as background.
- ELEXSYS E 500 EPR X-band spectrometer (Electron paramagnetic spectrometer) with visualEPR for visualisation
- Spin trap: PBN, N-tert-butyl-α-phenylnitrone
- Kessil lamps: 370 nm, 427 nm, 467 nm, 525 nm



PBN-Cl side reaction



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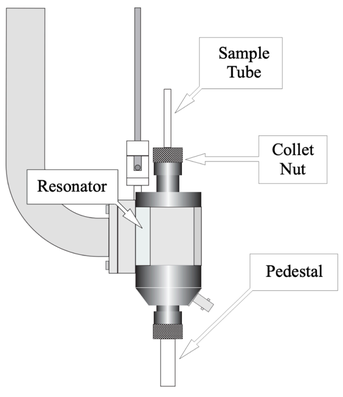

CONCLUSIONS

- HLF reaction works
- Reactive intermediates cannot be caught without PBN
- Short lifetime of reactive intermediates
- PBN captures all radicals; w/ chlorine - very fast reaction
- Difficult to see the N-radical and the conversion of N- to C-radical
- (co)excess of PBN leads to reactions of PBN with itself
- Future attempts will be made to trap N-radicals by freezing in a finger-dewar