

# Effects of an rearrangement reaction on the product distribution of the Hofmann-Löffler-Freytag reaction

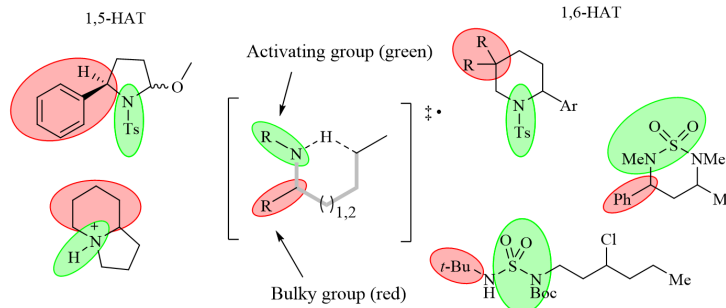
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- Hofmann-Löffler-Freytag reaction is a well known reaction for C-H activation via N-centered radical generation and subsequent rearrangement to C5 or C6 radicals.
- However, effect of positioning activating and/or bulky groups endo or exo with respect to the 1,5-HAT and 1,6-HAT transition states has not been examined in a deep and thorough manner.



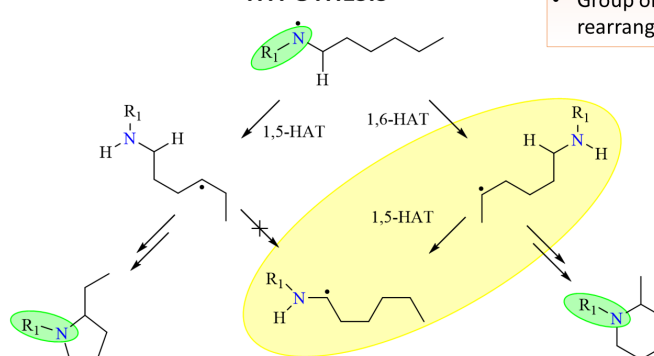
- Activating group endo guides the product distribution in such a manner that a predominant piperidine product is formed.
- When C5-radical  $\approx$  C6-radical stability.
- Intermolecular piperidine formation proposed when C6-radical more stable than C5-radical, with activating group exo.
- Activating group endo leads to an intramolecular 1,6-HAT and piperidine formation.
- Pyrrolidine ring is obtained, when stability of C5-radical is greater than C6-radical and activating group is exo.
- Effect of bulky groups exo and endo; Thorpe-Ingold effect.
- Group on C2-position may block unwanted rearrangement.

	TS	PIC	TS	PIC
	1,5-HAT	68.51	31.75	
	1,6-HAT	56.04	30.35	43.73 10.29
C6 $\Rightarrow$ C2 radical				
	1,5-HAT	81.47	38.46	
	1,6-HAT	62.67	27.49	42.63 -13.55
	1,5-HAT	70.07	30.89	/
	1,6-HAT	77.18	44.54	/
	1,5-HAT	36.99	-22.24	
	1,6-HAT	26.43	-26.13	46.99 -37.70
	1,5-HAT	42.98	-19.16	/
	1,6-HAT	34.35	-22.37	/
	1,5-HAT	61.30	-6.21	/
	1,6-HAT	48.71	-11.61	/
	1,5-HAT	32.26	-24.84	/
	1,6-HAT	50.06	-16.11	/

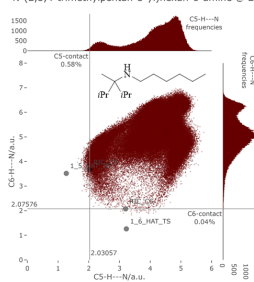
## Methods

- GaussView, IQmol
- Gaussian 16 opt+freq+IRC @B3LYP/6-31G(d)
- XTB 6.41. CREST, MD @GFN-2-xtb
- Klaster Isabella @SRCE
- Klaster sw.pharma.hr, Farmlnova @FBF

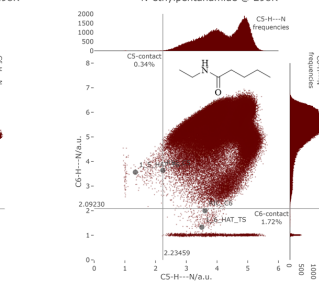
## HYPOTHESIS



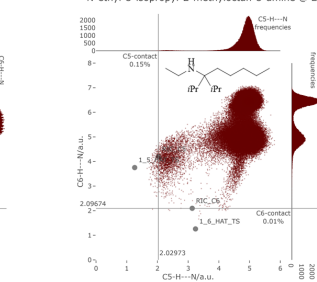
N-(2,3,4-trimethylpentan-3-yl)hexan-1-amine @ 298K



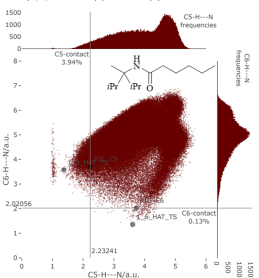
N-ethylpentanamide @ 298K



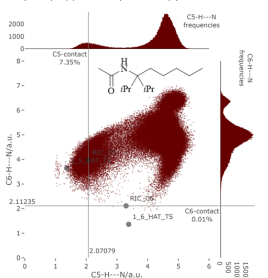
N-ethyl-3-isopropyl-2-methyloctan-3-amine @ 298K



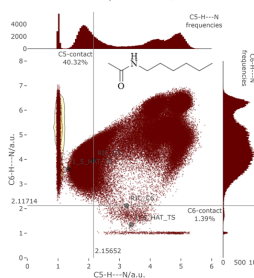
N-(2,3,4-trimethylpentan-3-yl)hexanamide @ 298K



N-(3-isopropyl-2-methyloctan-3-yl)acetamide @ 298K



N-hexylacetamide @ 298K



## Conclusion

- Activating group exo or endo  $\Rightarrow$  1,6-HAT process.
- Bulky group endo  $\Rightarrow$  1,5-HAT process.
- Bulky group exo  $\Rightarrow$  1,6-HAT process.
- Unless C2 position is blocked; C6 radical  $\Rightarrow$  C2-radical
- Bulky group exo & activating group endo  $\Rightarrow$  1,6-HAT, in accordance with results produced by Short et al.<sup>3</sup>
- Bulky group endo & activating group exo  $\Rightarrow$  1,5-HAT process.

## References

- M. A. Short, M. F. Shehata, M. A. Sanders, J. L. Roizen, *Chem. Sci.* **11** (2020) 217–223.
- D. Šakić, H. Zipse, *Adv. Synth. Catal.* **358** (2016) 3983–3991.
- T. Duhamel, M. D. Martínez, I. K. Sideri, K. Muñoz, *ACS Catal.* **9** (2019) 7741–7745.
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- E. Del Castillo, K. Muñoz, *Org. Lett.* **21** (2019) 705–708.

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Light-driven functionalization of Unreactive sites  
Using Oxidative Amination

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