

# Referee's report on PhD thesis

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## New Carbanion Rearrangement of Sulfur Compounds and Its Application

The presented thesis describes work on two main projects. The first was to use Julia olefination reaction in development of improved methods for preparation of several compounds which belong to the group of naturally occurring cyclopentanoid monoterpenes – iridoids. During this work an interesting phenomena was encountered during lithiation of aryl alkyl sulfones used in Julia reaction – instead of deprotonation of  $\alpha$ -carbon in alkyl group, which is more acidic, the *ortho*-carbon in the aryl group was deprotonated, but rearrangement to the expected  $\alpha$ -deprotonated product could also be observed. The study of this phenomena became a second project – its scope and limitations and mechanism of the *ortho*- $\alpha$  rearrangement were studied and described in detail. The results of this study were then also utilized in the first project in Julia olefination reaction used in total synthesis of the selected iridoids

Theoretical part of the thesis describes sufficiently the present status in the areas of iridoids and their syntheses, reactivity of sulfones and sulfoxides towards bases, and Julia olefination. In the first part of Results the preparation of series of different alkyl aryl sulfones and sulfoxides is described, as well as selectivity of their lithiation and mechanism of *ortho*- $\alpha$  transmetalation. A number of experiments was done to elucidate the mechanism of this rearrangement including kinetic experiments, study of kinetic isotope effect, preparation of precursors for crossover experiments and performing the crossover experiments. The second part of Results then describes really improved ten step syntheses of two iridoids with overall yields around 20%. In Experimental part are well described all procedures used in the experiments and all new compounds very well characterized ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR with signal assignments, IR, m.p., MS, elemental analysis or HRMS, specific rotation,  $R_F$ ).

Nevertheless, I have some comments and recommendations for the author:

- I do not consider the chosen method for numbering of compounds to be the best one. Mainly the presence of a hyphen in the number is confusing due to the author's method for expressing ranges of compound, which also contains a hyphen. One ugly example of the result of those rules is: 1-2a-c, almost illegible for a casual reader. I would recommend to use e.g. 1-2a–1-2c (dash instead of hyphen for a range, using the whole numbers), or ideally 1.2a–1.2c (dot instead of hyphen for a number).
- The Introduction chapter could have contain some information about methods for studying reaction mechanisms, about isotope kinetic effect and crossover experiments, which are important topics of the work.
- The first sentence below the Scheme 1.1 (page 19) is missing its beginning.
- In the Abbreviations – there should not be e.g. tBuLi (but only tBu) or TsOH (but only Ts). Some abbreviations are missing (iBu, DMPU, HMBC, HSQC, ATR, Ac, Et, Me) or are used in different meanings (TMS - trimethylsilyl, tetramethylsilane). Preferred term for  $R_f$  in the used contexts is "retardation factor" (not "retention factor", see IUPAC Gold Book).
- The legend for Figure 3.4 (page 51) does not clearly describe what values are in the graph (Figure 3.1 explains it much better).
- In experimental part - generic part - the sources of used commercial chemicals were not mentioned as well as detection methods for TLC. In characterizations of

compounds prepared by some general method it would have been more convenient for readers to specify for each compound by which general method it was prepared.

There are also some questions for discussion:

- Could the methanolate anion 133a (page 7) really exist in the presented forms?
- What were the decomposition products of the compound 1-2a (Scheme 1.2, page 20) in the attempts for reduction with  $\text{LiAlH}_4 + \text{TiCl}_4$ ?
- What was the reasoning behind the addition of given number of equivalents - 2 eq of TMEDA or 6 eq of HMPA - to the reaction mixtures? Were other ratios of the additives studied?
- How do you explain the lower extent of the overall lithiation of sulfone 1-2c (page 22) at higher temperatures?
- Should the products of the reaction shown in Table 1.8 (page 31) really contain OH groups (supposing no workup was done)?
- What is the exact mechanism of formation of the compound 2-5 shown in Table 2.4 (page 39). Is the structure correct?
- In Table 2.2 (page 37) – what is the electrophile from  $\text{B}(\text{OMe})_3$ , is it really  $\text{B}(\text{OH})_2$ ?
- $R_f = 0.00$  is given for compound 4-52. Why some elution mixture, which would give a reasonable  $R_f$  value, was not used?

Despite the above critical comments I consider the thesis to be well written and the results are interesting. Its quality was also confirmed by two papers related directly to this work (published in impacted journal) in which Lucie Řehová is the first author. In addition Lucie Řehová is also co-author of another publication and presented her work on several conferences in forms of poster or oral presentation. Therefore I recommend the thesis for defense.

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