Olga Bakhanovich:
Synthesis of *N*-(per)fluoroalkyl azoles by rhodium(II)-catalyzed transannulation of *N*-(per)fluororoalkyl-1,2,3-triazoles
PhD Disertation

The thesis aimed at the development of a new methodology for the construction of *N*-(per)fluroalkyl pyrroles and indoles. Pyrrole derivatives arise from the rhodium(II)-catalyzed reaction of *N*-R_f triazoles with terminal acetylenes, which involves opening of the triazole ring, extrusion of dinitrogen (N_2), insertion of acetylene into the metallocarbene intermediate, cyclization, and recovery of the catalyst (Scheme 32). A new mechanism for this transformation is proposed, which explains the formation of positional isomers. Interestingly, alkylacetylenes R–C≡CH were found to exhibit much better positional selectivity than their aromatic congeners Ar–C≡CH. A related Rh-catalyzed reaction of cyclohexenyl triazoles, echoing Nazarov cyclization, was found to produce *N*-R_f tetrahydroindoles that can be converted into fully aromatic *N*-R_f indoles on a redox reaction with DDQ. A plausible mechanism was proposed (Scheme 41). These methods, for which the term "transannulation" was coined, were expected to pave an unorthodox avenue toward novel molecules, potentially with interesting biological implications. Reactivity of the indoles, obtained via this methodology, was briefly explored: bromination, lithiation/carboxylation, and Friedel-Crafts acylation. The resulting products are expected to become useful building blocks for further synthetic endeavors.

This uncharted area was experimentally very demanding, with a number of reactions giving mixtures of volatile isomers, difficult to isolate and separate. As a result, the printed version of the thesis may seem rather thin but one has to take into account the experimental difficulties.

The candidate's English would require improvements; proof-reading by a native speaker would have been beneficial. This would have eliminated the use of incorrect prepositions or words, or clumsy expressions, e.g., "…synthesis of the *scope* of triazoles" (p. 32, 36, and elsewhere), or "…elimination produced the product" (p. 29). "Isolated yield" is a common nonsense that has infested the literature in spite of the crusading efforts of journal editors, in particular of Scott Denmark.

The proposed mechanism for the Rh-catalyzed addition of acetylenes to *N*-R_f triazoles (Scheme 32, p. 40) was inspired by that proposed for the *N*-tosyl analog in ref 44. The present mechanism for the *N*-R_f substrates suggests an intervention of cyclopropene intermediates **C**, which can rationalize the formation of regioisomers, not observed with *N*-tosyl triazoles.

Regarding the characterization of individual compounds: IR spectra are not reported at all, not even for compounds with significant functional group (C=O, C≡N, CO_2H). In the ^{13}C NMR spectra, the number of peaks does not always correspond to the number of carbons, e.g., for **42a'**, **43*l***, **43m**, **43n**, **43o**, and **44**. Integration of the ^{1}H NMR spectra occasionally gives a count that differs from the expected number of protons, e.g., for **42a** and **43m**. HRMS spectra are mostly shown for isomeric mixtures (**42a**, **43a**, **43d** and **43m**) and one is not reported at all (**49f**). Using the *JOC Compound Characterization List* would have helped here. Furthermore, *JOC* and other journals normally require both the weight and percentage yields; in this thesis only the percentages are given, which I find insufficient.

Questions:

(1) What is the role of the phase-transfer catalyst in the NaH-mediated *N*-alkylation of indole in DMF (p. 23)?

(2) In Scheme 23 (p. 29) the last reaction gives oxazole that contains one more carbon atom than the starting component. What is its origin?

(3) The preparation of cyclohexenylacetylenes (Scheme 37, p. 48) obviously calls for the Sonogashira coupling, which would circumvent the chemoselectivity problems associated with the use of Grignard reagents. Why wasn't this attempted?

(4) Aromatization of the tetrahydroindole derivative **48k** using DDQ is understandable (Scheme 43, p. 52). However, further oxidation of the propyl sidechain to produce enal **49k'** is amazing. Is there any precedent? If this is a new reaction, it would deserve mechanistic comments and further development. Interestingly, according to the scheme, **49k'** is obtained in 30% yield, whereas the Experimental gives 50%. Which one is correct?

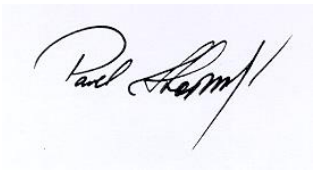
(5) The reaction of the *t*–Bu-indole **49f** with $AcCl/AlCl_3$, giving the acylated product **53** (Scheme 47, p. 55), can hardly be regarded as an example of S_N1. Will you please propose a more plausible mechanism?

(6) Scheme 49 (p. 56) shows 1 equiv of NCS, whereas the comment below says 2 equivs. Which one is correct? In the same scheme, yield is given only for the first reaction, while for the 2^{nd} and 4^{th} reactions only product ratios are shown. What were the yields?

(7) Does *N*-CF_3-indole (**49a**) smell nice?

Overall: Beyond doubt this was an experimentally very difficult project and the candidate did a good job. However, partial lack of attention to detail, together with some negligence, reduces the final effect.

Conclusion: Despite some reservations, I can confirm that the candidate has demonstrated her ability to carry out independent research and to write about it. Her work will undoubtedly inspire others and her methodology is likely to be implemented in the synthesis of functional molecules. Therefore, I **recommend** that Ms Bakhanovich be awarded a **PhD**.



Pavel Kočovský