Ph.D. Thesis of Prabhakar Cherkupally - a review

The Thesis, "Synthesis and Application of Fluorophophonates", are comprised of work realized by the candidate at the Institute of Organic Chemistry of the AS CR in the group of Dr. Petr Beier. The Thesis are longer than 160 pages and four papers in peer-reviewed journals have been published on the basis of presented data. As scientific value of candidate's work has already been evaluated by the journal reviewers, my task as reviewer of the Thesis is simplified. Thus, in addition, I checked the formal points and I would have some questions for a discussion.

Generally, I very appreciated the "Introduction" containing a comprehensive review of fluorination and fluromethylation methods as well as information on chemistry and utilizations of fluorinated phosphonates and phosphonic acids. The "Results and Discussion" part is divided according the published papers and some unpublished work (Chapter 3.5), results are intelligibly explained and discussed. The experimental part brings complete experimental details for the prepared compounds. In the Conclusions, I somewhat missed a more concise comparison of the methods introduced in this Thesis with those already known for synthesis of the same or similar products; it could be summarized in the talk during defence itself. The Thesis is nicely readable and contains minimum English/printing errors.

Some formal matters.

1) I was surprised that list of abbreviations (pp. viii–x) contains nomenclature errors. On the other hand, some abbreviations are not listed, e.g. diglyme, DME.

2) The ^{31}P NMR probably everywhere means ^{31}P{^{1}H} NMR but it is said only in the Experimental and, thus, valid only for this part.

3) Some other compound names in the text are incorrect.

Some more specific points:

- p. 41, 2nd paragraph. Phosphodiester moiety does not have formula/charge " $(PO_4)^{2-}$ ".
- p. 44, Scheme I.24, 2nd reaction. The fluoro reagent has incorrect formula.
- p. 48, Scheme I.31, caption. There are not only keto-phosphonates in the Scheme.
- p. 79, Figure 3.1. The formula of ferrocenium hexafluorophosphate is incorrect.
- p. 84, last line. Concentration of H_3PO_4 is not given.

None of these formal inaccuracies is so important to be corrected in the already printed text of the Thesis.

Some, mostly general, questions.

1) Page 60, Scheme 3.3. Was the reaction progress followed in-situ over the reaction time (e.g. by ^{31}P and/or ^{19}F NMR, GC...) to prove the proposed mechanism?

2) Page 67. There is a statement that one transition state is lower in energy than the other one. Is the statement supported by calculations? If yes, what is the difference in energy, for which "**R**'s" was the energy calculated?

3) Chapter 3.3. There are other additives to change reactivity of organolithium reagents, e.g. amines as *N*,*N*,*N*¢,*N*¢-tetramethyl-ethylenediamine. What would be the effect of this class of additives?

4) Page 76, Table 3.8. β-aminoalkylphosphonic acid are known as biologically active compounds but mostly with aliphatic chains on β-carbon atom. Was more aliphatic aldimines considered/tested in the reaction besides that with *i*-propyl substituent? Or with other *N*-protecting groups?

5) p. 82, Scheme 3.12. Can the mechanism be proved e.g. by trapping the CF_2 species?

6) Through the text - only diethyl phosphonates were used. However, properties of phosphorus acid esters can be tuned, even more finally than those of carboxylate esters, by kind of the ester groups. Were other esters considered/tested in the reactions? What could be their effect?

In summery, the work fulfils requirements for PhD theses and I do recommend to accept the presented work for the PhD defence.

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