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Reviewer report on the PhD thesis submitted by Ms Monika Skibińska

With the view to obtaining the doctoral degrees of Paris-Saclay University (France) and Adam Mickiewicz University (Poznań, Poland), Ms Monika Skibińska has prepared and submitted a doctoral dissertation entitled "Synthesis and reactivity of trifluoromethylated aziridines and β-lactams containing phosphonate moiety". Her work was co-supervised by Dr Benoît Crousse in France and by Prof. Henryk Koroniak and Dr Tomasz Cytlak in Poland. Her manuscript is a 186-page document, which is organised as follows: (i) a short opening section containing a table of contents, a table of abbreviations and a preamble; (ii) a short introductory section on the introduction of fluorine-containing groups or phosphonate esters in organic molecules (Chapter I); (iii) two large chapters providing a detailed account on the investigations carried out by the candidate in the fields of trifluoromethyl-substituted aziridine and trifluoromethyl-substituted β-lactam derivatives, respectively (Chapters II and III); (iv) a full experimental part for these two chapters. The dissertation ends with a reference section (263 entries), a summary of Ms Monika Skibińska's achievements (scientific production, participation to conferences, internships); and finally, one-page abstracts in three languages: Polish, French and English.

The initial bibliographical section (Chapter I) is a brief general review on the main fluorine-containing groups (in particular, trifluoromethyl and 1,1-difluorovinyl) and on their importance, as well as on the relevance of phosphonic esters and amides in biologically active molecules. This part is well written and highlights the main points that are useful to know with respect to this chemistry.

Chapter II (34 pages) constitutes the first part of the Results and Discussion section. It is focused on CF_3-substituted aziridines fitted with a phosphonate functional group. Accordingly, some state-of-the-art is first given on all the concepts that are necessary for understanding this chapter. This begins with an introduction to aziridine chemistry (structure, reactivity, usual protecting groups). The specific case

of aziridine derivatives having a CF_3 group and a carbonyl-based substituent is then presented, as well as the various synthetic routes to these compounds. General interest both for CF_3-substituted aziridines and for phosphonated aziridines is then highlighted, leading to the idea of associating both types of functional groups, which has been rarely done in the past. This context being introduced, two main families of CF_3-substituted aziridines having a phosphonate group are targeted, depending on the substituent at the nitrogen atom: a benzyl group or an electron-withdrawing group such as a Cbz or a Boc group. The study of the reactivity of these aziridines, especially nucleophilic ring-opening reactions, is also part of the work programme.

Attempts at performing nucleophilic ring-opening reactions of *N*-Bn-substituted aziridines with amines led to the discovery of an interesting rearrangement that afforded a functionalised vinyl phosphate compound, upon simple treatment with potassium carbonate. Using a stronger nucleophile (a deprotonated sulphonamide), an apparent nucleophilic substitution reaction did take place but at an unexpected position, α to the phosphonate group, displacing the hydroxyl group rather than opening the aziridine ring, which was left unscathed. Such a process was surprising under the reaction conditions applied and a rather extensive and impressive mechanistic study was undertaken. This led to the proposal of a convincing mechanism involving an aldehyde intermediate, which was the very precursor of the alcohol starting material. The preparations of the corresponding free aziridine and the *N*-Cbz- or *N*-Boc-substituted derivatives are then described, with further interesting unexpected observations. Indeed, when nucleophilic aziridine-ring opening was attempted with the *N*-Cbz-protected diastereoisomeric mixture of substrates, another type of unanticipated process, namely an aza-Payne rearrangement, was observed and carefully studied.

The next chapter, chapter III, is, with 77 pages, the largest of the manuscript. This is due to the fact that although it deals entirely with CF_3-substituted β-lactam compounds, it is actually delineated along three sub-projects: the first one is devoted to the synthesis of various CF_3-substituted β-lactams having various substituents at the nitrogen atom, and the investigation of the problem of the selective further functionalisation at the α position relative to the carbonyl group. The next sub-project goes one step further and aims at the synthesis of β-lactams bearing a trifluoromethyl group at position 4 and also fitted with a phosphonic ester group, which may be located at more or less remote places, onto the β-lactam ring or on a side-chain at position 3. The last part focuses on the problem of the transformation of the CF_3-substituted β-lactam products into a family of *β,β*-difluoroenamides having the C=C double bond in exocyclic position.

For each of these subsections, the same organisation as in the preceding chapter has been elected: some literature insight is first given, from a broader perspective to more focused data. The goals of the sub-project are then carefully presented. A detailed account of the investigations that have been carried out follows, with a mechanistic discussion wherever this is relevant. Finally, the main results are summarised and perspectives are suggested in terms of future possible developments or applications.

Concerning the first sub-project, Reformatsky-type reactions were applied successfully for the preparation of the target compounds, after some optimisation. They are involving three different CF_3-substituted imines as the electrophiles. For extra functionalisation, enolate chemistry was then explored. The best conditions identified require the use of 1.5 equivalents of LiHMDS at −25 °C, in THF. Several aldehydes could be employed as the trapping electrophiles. The use of alkyl halides or ethyl chloroformate led to the production of dialkylated products, at least in part. To turn this observation to her advantage, the PhD candidate underwent a related study with substrates already having one substituent at position C3, α to the carbonyl group of the β-lactam ring. Enolate formation and trapping with various electrophiles allowed the controlled formation of highly substituted β-lactam products, with excellent diastereoselectivity. Finally, deprotection of the nitrogen atom, using CAN, was demonstrated in the case of substrates having a 4-methoxyphenyl group.

For the second sub-project, a few different methods were explored. Again, enolate generation with LiHMDS gave good results; trapping with diethyl chlorophosphate produced several of the targeted molecules, with very high diastereoselectivity. However, this success could not be extended to reach all of the goals initially proposed, which highlights the difficulty of this chemistry.

In the last sub-project, the formation of *β*,*β*-difluoroenamides by dehydrofluorination of 4-CF_3-substituted β-lactams proved to be feasible, albeit only when the α position relative to the carbonyl group was fully substituted, and using 4 to 5 equivalents of LiHMDS. These reactions proceeded in typically moderate yields. In the case of a substrate having two ethyloxycarbonyl groups at position 3, an interesting unexpected formal migration of one of the two ester groups was observed. A reasonable mechanism is proposed to explain this process. At the end of this part of the work, the problem of the subsequent deprotection of the nitrogen atom remains to be solved, at least in the *N*-PMP series. Perhaps other protecting groups would lend themselves better to this operation.

The experimental section opens with some general considerations (section IV) and then presents the experimental protocols and characterisation data associated with all the work, in substantial detail. This section (V) is organised according to the various parts of the project, previously discussed in chapters II and III. The experiments are described in such a way that they can certainly be reproduced. All the new compounds are generally very well described. It is worthy of note that wherever relevant, the reported information includes ^{19}F and ^{31}P NMR data.

Overall, Ms Monika Skibińska's dissertation is very well organised and presented. It must be noted that it contains a number of grammatical mistakes but this does not disturb reading so much and one should keep in mind that the author's native language is not English. With this respect, her efforts are greatly appreciated. Besides, the text is perfectly understandable throughout the manuscript. Notwithstanding this formal aspect, the following points underline the high quality of this work: (i) during the discussion, some reference to literature work was sometimes necessary and the candidate made the choice to present this information in separate boxes. This is an excellent idea that ensures that no confusion can be made between the discussion itself and the literature data. Furthermore, the examples presented are always relevant and truly help understanding the results. (ii) The scientific thinking process followed by Ms Skibińska is particularly well explained: when reactions take a different course from the one that had been anticipated, the reader is presented with the various pieces of evidence, especially observations by NMR, that are leading to conclusions concerning the structures of the products actually obtained. (iii) Every time, care is taken to propose reasonable mechanisms that can account for such unanticipated results. (iv) As already mentioned, the goals of each separate sub-project are clearly introduced and the corresponding results are clearly and carefully summarised. All of this makes this manuscript particularly pleasant to read. Perhaps, a general conclusion on the whole PhD work, with some perspectives, would have been an additional good point.

The sum of the results obtained is impressive. They are highly valuable and it is appreciated that the corresponding investigations have required skill, rigour, time and energy. Some of the compounds under study are not easy to work with and it is clear that the candidate has learnt a lot while working on this PhD project. She has had the opportunity to perform a wide range of different chemical reactions and to analyse various types of NMR spectra. She has acquired expertise in all of these fields and in the associated techniques. To conclude, **my opinion is that Ms Monika Skibińska's PhD dissertation and results are of high quality and that her defence can be allowed to take place**.

Here are selected questions that may be answered by the candidate during the defence:

– Page 45, Scheme 31.

The mechanism displayed on this scheme looks reasonable. Can you think of further experiments that could support it further? For instance, what would happen starting from a 50:50 mixture of two alcohols: this one, **126ab**, and another one, having a different substituent at the nitrogen aziridine (for instance a PMB group) and a different phosphonic ester moiety (for instance a dimethyl phosphonate)?

– Pages 77–78, Table 5.

In your opinion, why do aldehydes lead to mono-substituted products, while the use of other electrophiles results in di-substituted products, at least in part?

– Experimental part, p. 158, compound **266**.

Can you comment on the description of the ^{1}H NMR signal at 2.97 ppm? Why should it appear as a doublet of doublets, with such an unusual coupling constant of 93 Hz? Would a description as an AB system not apply in this case?

[Similar questions could be asked about the signal at 3.06 ppm of compound **451**, p. 171 (and perhaps elsewhere)].

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