

The submitted thesis presents comprehensive mechanistic investigation of rearrangements of substituted isothiuronium salts. The author focused on two main series of substrates: isothiuronium salts **1** derived from 2-bromobutyrolactones and isothiuronium salts **3**, **5**, **7** and **9** derived from 3-bromophthalides. In the latter case, the mechanism of rearrangement was studied separately for unsubstituted, monosubstituted and *N,N'*-disubstituted isothiuronium salts.

The mechanisms of rearrangements were studied using standard approach, i.e. by the measurement of the kinetics under different conditions accompanied by the measurement of  $pK_a$  of the substrates and investigation of the substitution effect. In the particular cases, intermediates of transformations were detected by spectroscopic methods, proved by derivatization or predicted by calculations to support the proposed mechanism. As an example, I would like to point out trapping of aldehyde **IX**, intermediate of transformation of non-substituted salts **1**, with *N,N*-dimethylhydrazine. I appreciate also combination of several non-direct evidences to support double-displacement mechanism in the case of *N,N'*-disubstituted isothiuronium salts **9**. Author used measurement of the effect of nucleophile type and its concentration on the rate of rearrangement, trapping of carboxylic acid intermediate **XXVII** by methyl iodide or negative checking of S- to N- migration with six membered lactone **12c**. It was accompanied by measurement and calculation of IRMPD spectra. Unfortunately, the last evidence about stereochemical control of transformation of salts **9** could not be done due to low stability of isothiuronium salts. But it is understandable.

In summary, mechanisms of rearrangement of three different isothiuronium salts were proposed and proved in the thesis. Moreover effect of Cu(II) ions on the mechanism was studied. Thesis is well written almost without typing errors. All conclusions are well documented by experimental data. The prepared compounds are characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, elemental analysis and in some cases by HR-MS. I appreciate quality of Schemes and Figures as well as existence of the list of compounds which is helpful mainly in the discussion of the kinetic results. The results were published in two original papers, I think that there are interesting data for next manuscript in the thesis. In the list below, I collected recommendations and specific comments which are mainly topics for discussion during defence.

#### Specific Comments:

- Author mentioned many attempts to prepare non-racemic salts **9** which could be used to study racemisation. Has author tried to separate stereoisomers in the form of diastereomeric salts with chiral anion?
- The conclusion about configuration *E* of compound **2g** in the solution based only on observation of one set of signals in NMR is questionable (page 52). Configuration could be *Z*, which is, moreover, in accordance with x-ray structure! Have author made any other attempt to determine the configuration of **2g** in the solution (e.g. NOE etc.) ? I am aware that it is not trivial in such a case of compounds.

- Is there any reason to use non-linear function for the data at pH 5.52 at low concentrations of buffer (Figure 14)? It could be linear, similarly as dependence for pD 5.14 in Figure 12. On the other hand, both dependences could be non-linear. How to decide it?
- Significant deviations from Hammett dependences were observed for methoxy derivatives of **3**, **7** and **9**. However, Hammett constant for derivatives **9** was determined from the only two points. Is it correct? The highest deviation was observed for methoxy derivative **7b**. Author tried to explain this phenomenon by tautomerism. Could NMR or spectrophotometric titration help to elucidate it? If the value of Hammett constant for acidity of **7** is around 5, hypothetical nitro derivative should have pK<sub>a</sub> approximately 1.5. Is it possible?
- Can author comment very low value of pK<sub>a</sub> for **9e** determined by potentiometric titration? Comment to two values of pK<sub>a</sub> in the case of **9c** is also desirable.
- Abbreviation "M" is recommended in place of "Me" for metal, especially when author uses "Me" for methyl group (e.g. see Schemes 5 and 6).
- p.21 line 9 Phthalaldehydic acid in place of "alkyl halide"
- Formulae of **1i**, **1j**, **2i** and **2j** in Scheme 38 are not in accordance with those in the list of compounds; **1i** does not correspond to the x-ray structure depicted in Figure 10. Formulae of the products of the second reaction in the Scheme 38 do not correspond with description "**2l-n**" and "**2h-k**".
- The described (p. 69) shape of  $k_{\text{obs}}$  vs  $c_{\text{Cu}}$  dependencies is not in accord with data in the Figure 18.
- Four points are shown for salts **7** in the Figure 26 but only three points are explained.
- It seems to be trivial but I miss comment to the preparation of thioureas in Experimental.

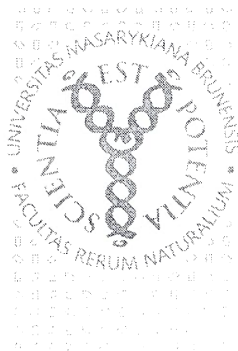
**Evaluation:**

I would like to conclude that the above mentioned comments are only marginal and the PhD. thesis is at a high level. Thus, I strongly recommend **PhD. thesis to be accepted** and doctoral degree to be awarded to author after successful defence.

Prague, February 6<sup>th</sup>



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## Oponentský posudek disertační práce

Autor: Ing. Jiří Váňa

Název práce: Studium transformačních reakcí isothiuroniových solí odvozených od bromlaktonů

Předložená práce se zabývá syntézou a studiem mechanismů reakcí isothiuroniových solí, které vedou k substituovaným thiazolidinonům, případně isoindolkarbothioamidům. Disertační práce v rozsahu 152 stran je rozdělena do 4 kapitol, které zahrnují úvod do problematiky, literární rešerši a vlastní výsledky výzkumu. Po vstupní kapitole autor uvádí čtenáře v literární části (kapitole 2) do problematiky reakcí thiomčoviny, reakcí katalyzovaných přechodnými kovy a velmi přehledně shrnuje poznatky o mechanismu nukleofilní substituce alifatických sloučenin, včetně enzymy katalyzované nukleofilní substituce. Třetí kapitola jsou výsledky a diskuse související s vlastním výzkumem a čtvrtá kapitola jsou experimentální data. Na závěr uvádí Ing. Váňa užitečný seznam struktur, který slouží k snadné orientaci při čtení textu.

Svým obsahem se práce dotýká aktuální a rozvíjející se oblasti chemie, která na modelových sloučeninách zkoumá mechanismy enzymatických procesů. Jejím cílem bylo syntetizovat řadu isothiuroniových solí a studovat kinetiku jejich reakcí za účelem navrhnout odpovídající reakční mechanismy.

Pro studium mechanismu autor využil pestrou škálu užitečných kinetických a fyzikálně-chemických experimentálních technik, včetně studia KIE, a LFER, NMR, RTG analýz. Kromě toho jsou výsledky doplněny kvantově-chemickými výpočty. Kombinace výsledků obdržených díky těmto metodám je zpracována na velmi vysoké profesionální úrovni. Z textu DP mi není jasné, zdali veškerou práci udělal doktorand sám, nebo jsou zde uvedeny i výsledky některého ze spolupracovníků. Prosím o informaci v tomto ohledu.

K disertační práci jsou přiloženy dvě publikace uveřejněné v *J. Heterocyclic. Chem.* a *J. Org. Chem.*, ve kterých je Ing. Váňa uveden jako první autor. Jen jedna z těchto prací je pouze jednou v textu citována (str. 86) a tak postrádám v DP upozornění na souvislost s přiloženými články. V rámci této poznámky bych se proto rád zeptal, zdali se připravují ještě nějaké publikace založené na výsledcích získaných v průběhu studia doktoranda.



## **Examiners Comments-PhD Thesis- Jiří Váňa –January 15<sup>th</sup> 2012.**

### **Title:**

**Mechanism of ring transformations of isothiuronium salts derived from bromolactones-  
University of Pardubice**

**Examiner: Dr Andrew Laws**

### **General Comments:**

The thesis describes mechanistic studies which have been undertaken in order to determine the detailed pathway by which a series of isothiuronium salts undergo ring closure reactions. These reactions proceed via nucleophilic substitution, the kinetic investigations have determined both the molecularity of the reactions and the stereochemistry of the attack i.e. front versus back side attack. The work reported by Jiří is separated into two sections: the first describes the rearrangement of S-(2-oxatetrahydrofuran-3-yl)-N-(4-methoxyphenyl)isothiuronium bromide into 5-(2-hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one; the second describes the synthesis of a significant number of substituted S-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)isothiuronium bromides and studies of their rearrangement to either carbothioamides or thioureas. The science described in the first part of this work is extremely good and has provided a number of novel results which have been published. The quality of this work and the robustness of the results that have been described in the first half of chapter three are suitable for the award of PhD. The results for the second part of the research programme are equally interesting and are also novel. The discussion of this work, whilst being robust, does raise a number of questions and there may be alternative potential explanations for the Hammett correlations that have been reported by Jiri. These alternative explanations are described below and could usefully be discussed in the oral examination.

It is clear that a large amount of synthetic work has been undertaken as part of this research programme; most notably this includes the synthesis of reagents 2a-2p (for the first section) and 3a-3d, 5a,b, 7a-7e, 9a-9J (for the second section). It is not always clear which molecules are being reported for the first time and this needs to be highlighted in both the summary and also in the synthetic section of the experimental.

The referee is very grateful that Jiří has chosen to write his thesis in English and, on the whole, this has been done to a very good standard; he should be congratulated on this being the case. There are still a number of typographical and grammatical errors, rather than provide an exhaustive list of such errors in this report, this referee will provide an annotated copy of the thesis for the candidate at the time of the oral examination.

### **Detailed discussion of the thesis**

In a thesis submitted for examination in the UK it is common to provide, at the start of the thesis, a list of abbreviations and a list of figures that are used in the body of the thesis, it is also common practice to have at the end of a thesis, a separate chapter outlining the conclusions that have been

drawn from the work. It is not clear if this is required for a thesis submitted to the University of Pardubice and here the referee would like to seek the advice of other panel members.

### **Summary (Abstract)**

Again, this is very good and my only main slight criticism is that on the second page of the summary there is a need to include the exact names of the class of compounds used in part two of the investigation (substituted S-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)isothiuronium bromides). As the summary is often the only material that is universally available to read at external sites it needs to infer, in isolation, exactly what work has been undertaken, the statement that 3-bromophthalide (spelling is incorrect in thesis) derivatives have been prepared is too vague.

### **Introduction**

It is not clear why this is provided as a separate chapter. Is this a local requirement? Could it not be combined with chapter 2 as a first sub-heading? In the introduction there are various sections where hyphens and spaces are interchanged in the names of compounds, a typical example of this can be seen in the legend for scheme 1: - **3-yl) iso** should read **3-yl)iso** i.e. without a space.

### **Chapter 2 Theory**

Chapter 2 details the theory behind nucleophilic substitution reactions; this section is reasonably comprehensive and includes the underlying theory that supports the discussion that is presented in the following chapter. One small area that doesn't receive much attention is a discussion of some of the classical experiments, undertaken by Winstein, which provided evidence to support the existence of solvent separated ion-pairs. It would be reasonable to ask a question about this area at the viva-voce examination.

A number of the 'schemes' presented in chapter 2 require attention: Scheme 4 has BH<sub>3</sub>; schemes 6 and 7 have brackets separating resonance hybrids and Me being used as an abbreviation for metal where M would be more appropriate; in a number of schemes the curly arrows which are representative of the movement of electron pairs are not always clear e.g. in scheme 20 some arrows are missing and some appear to suggest movement of single electrons; scheme 30 has arrows moving in the wrong direction.

### **Chapter 3 (Results and Discussion)**

The first part of chapter 3 is very good, is extremely comprehensive and details the rearrangement reactions of isothiuronium salts containing butyrolactone motifs. It is clear that a very detailed kinetic investigation has been performed and the results of this investigation have allowed Jiri to develop the pH rate profile (figure 15). The subsequent discussion and development of a kinetic scheme that evolves from the simultaneous existence of T<sup>0</sup>, T<sup>+/-</sup> and T is very well constructed. My only very modest criticism of this section is that some of the figures are too small and I found it very difficult to see the full details of some graphs: this was especially true of figure 12 where I would have liked to have been able to determine some measure of the errors in the results by studying the variation in the values of the intercepts i.e., for the low pH buffers.

The second part of chapter 3 is also good and includes the preparation of a series of isothiuronium salts containing benzofuanones as the lactone-motif bonded through sulphur. The interpretation of the  $pK_a$  measurements and the subsequent analysis of substituent effects on the rates of rearrangements were undertaken by construction of Hammett plots and using  $\sigma_p$  values. A number of experimental details are missing in this part of the thesis that would allow the reader to get a better understanding of how the results were generated. It wasn't clear to this referee exactly how the data presented in figure 24 was used to determine the  $pK_a$  values that are presented in figure 25. There is no information about either the base or the substrate concentration used- in either the figure legends or in the experimental section –and it is therefore not possible for the reader of the thesis to be able to calculate the  $pK_a$  values-it might help readers to understand the information if these details were to be added.


It is unusual for the  $pK_a$  values to be so sensitive to what can only be described as a distant substituent and one that is isolated from the potential protonation sites by insulating  $sp^3$  hybridized methyne carbon. The referee would like to suggest that it might be worth exploring whether there are alternative explanations for these results, including consideration of the transmission of substituent effects by induction only with the use of  $\sigma_m$  values for correlating the kinetic constants.

#### **Chapter 4 Experimental Section**

This section is reasonably comprehensive. As discussed above, I would have liked to have seen some discussion of how the  $pK_a$  values were determined and I would also have liked to see some indication as to which compounds are being reported for the first time i.e. are novel. An indication of which spectra were recorded for which compounds would also have helped; this is especially true for **1a** to **1m** where only minimal ms/mpt data is provided. Where NMR data, both  $^{13}C$  data and  $^1H$  data, there is no indication as to which protons or carbons gives rise to specific signals and, as such, it would be useful to ask Jiří to assign a spectrum in his oral exam in order to clarify his understanding of the importance of this information.

#### **Overall Decision**

The work presented is of a high standard, the thesis contains a significant number of novel results and the discussion of these results expands knowledge; the thesis presented by Mr Jiří Váňa is suited to the award of PhD.



Dr Andrew Laws

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