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ARTICLE

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The Overman rearrangement is a very useful C-N bond forming reaction described for the first time in 1974. This transformation allows a chirality transfer with an excellent predictible induction, starting from a configurationally pure allylic alcohol, yielding in only one step to an amide moiety, via a [3,3]-sigmatropic rearrangement of an intermediate imidate. A recent valuable extension was developed by Chida and co-workers on orthoamide structures starting from allylic vicinal diols, avoiding time consuming protections. However, this attractive modified approach suffers generally from elevated temperatures, long reaction times and sometimes disappointing yields. To bridge this gap, we have carried out a combined experimental and theoretical study with the aim of elucidating the structures and the reactivities of these orthoamides. In order to rationalize the experimental results, it was first fundamental to identify the actual reactive species. The reactivity of these orthoamides has been then investigated. Theoretical calculations using Density Functional Theory (wB97X-D/ Def2TZVP method) have then been done in gas phase at 453 K to characterize the relevant chemical species (conformers of orthoamide diastereoisomers, prereactive complexes, and transition states structures) and to estimate the free energies of activation. The role of temperature has also been taken into consideration at 298K and 373K in comparison with 453K. A major contribution of the theoretical part of this study has been to show that the reactivity of orthoamides in the Overman rearrangement crucially depends on diastereoisomers present in the reaction media. Molecular simulation has allowed us to clarify the reasons behind the temperature requirements and the reaction time, tentatively helping chemists to understand their troubles in orthoamide Overman rearrangement.

Introduction

In the course of our studies on the synthesis of human neuraminidase 1 specific inhibitors,[1] one key transformation has been used a modified Overman rearrangement proposed by Chida's group ten years ago.[2] This reaction was performed onto orthoamides instead of imidates and benefits from time consuming protection steps.[3] However, as observed by the authors on several examples,[3-7] this process has proven rather difficult. In uncertainty, we have decided in this article to detail the mechanistic aspects and to carefully study the chances of success of the different steps involved in this Overman rearrangement.

Our study has decisively been extended to include molecular modelling investigations. In fact, orthoamides are recognized as reagents included in the portfolio of Overman rearrangements, yet questions remain concerning their structures as well as their behaviors in Overman rearrangements leading to the observed reactivities. Therefore, we have focused on understanding their structures and reactivities. The relative energies and conformer percentages have been computed to clarify the type of orthoamides that are present in the reaction media and to investigate the reaction mechanisms. From this, conclusions have been drawn concerning the mechanisms of the reactions, the role of temperature, and the origin of reactivity. This theoretical investigation is intended to rationalize, optimize, and extend our experimental observations.

A The Overman rearrangement, a sometimes demanding transformation

The Overman rearrangement[2] was described four decades ago as a [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates leading to allylic trichloroacetamides (Fig. 1), and this transformation has been applied to the synthesis of elaborated nitrogenated structures, like in cases of modified α-aminoacids **1**,[8] a substituted pyrrolidine **2**,[9] polyoxamic acid **3**,[10-12] a tetrodotoxin intermediate **4**,[13] and thymine polyoxin C **5**.[14]

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[b] Electronic Supplementary Information (ESI) available: Experimental procedures and NMR spectra for new compounds; Detailed discussion with modelling studies.

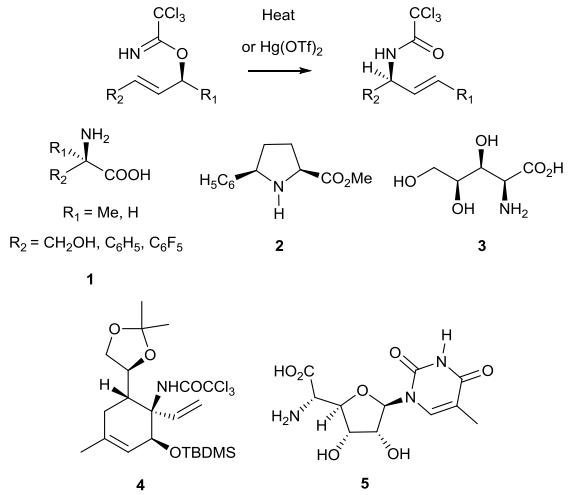

Fig. 1 The Overman rearrangement, as reported in 1974 and examples of chiral structures elaborated with this transformation
Ajouter l'abréviation de TBDMS

Cyclic structures, including unusual carbohydrates are the most common targets of traditional Overman rearrangement.[15-30] Overall, highly functionalized oxygenated structures require diverse drastic temperature conditions in aprotic high boiling points solvents, such as 165-180°C in dichlorobenzene or 220°C in *t*-butyl-benzene (in sealed tubes) or varying between 135°C under very low pressure (0.1 mm Hg) and 150°C in xylene. However, despite these harsh conditions, the product was sometimes obtained in low yields.

Consequently, two strategies have been developed to overcome these drawbacks. Replacing trichloroacetonitrile with trifluoroacetonitrile proved to be very efficient and yields were above 90%.[9-11,13] The major disadvantage of this method is the gaseous character of toxic trifluoroacetonitrile, nevertheless it is possible to use it as a solution in tetrahydrofuran.[10,31,32] In addition, Metz's group[33] described the Pd(II) catalysis offering another opportunity for improvement as excellent yields were obtained at room temperature for similar starting materials and Gonda's group has observed interesting results with microwave irradiation.[34,35] However, in our hands and on large scale, the Overman rearrangement remains a challenging transformation because of unreproducible results and handling difficulties with unusual reagents.

B The orthoamide Overman rearrangement

The major difficulty, when the Overman rearrangement is chosen as a key step in a total synthesis, relies on the necessity for the isolation of a specific alcohol, with orthogonal selective protections of other functions. The orthoamide Overman rearrangement, whose proposed mechanism appears in Figure 2, initially discovered by Vyas group[36] has been nicely applied by Chida's group as a key step in the total synthesis of broussonetine F,[3,4] sphingofungin F,[5,6] and kaitocephalin (Fig. 3),[7] and in the course of the synthesis of highly nitrogenated carbohydrates,[37] under high temperature conditions.

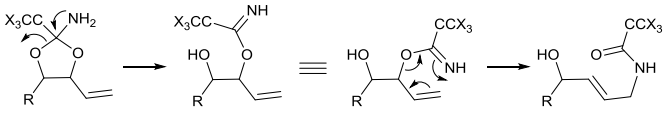

Fig. 2 Expected general mechanism for the orthoamide Overman rearrangement.

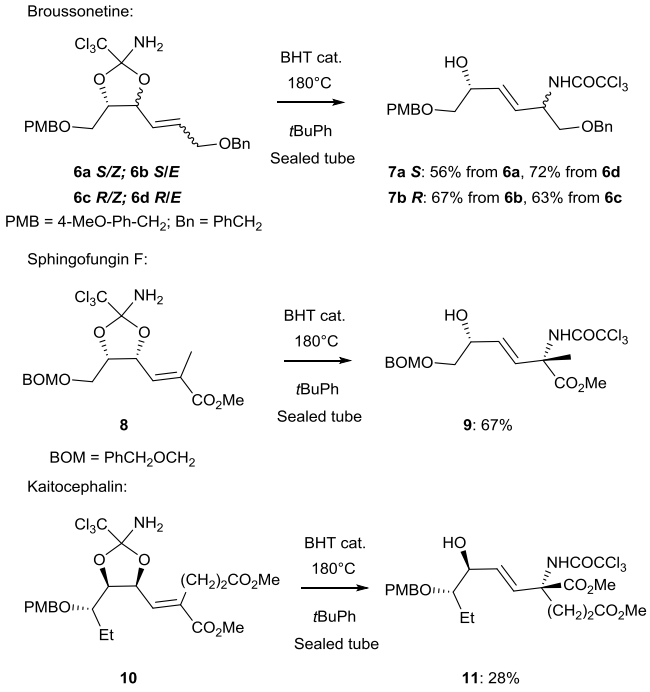

Fig. 3 Orthoamide Overman rearrangements in total synthesis.

Experimental results

Interested by the key step of the total synthesis of broussonetine F and especially by the transformation **6a** / **7a**,[3,4] we have synthesized the starting orthoamide **12** inspired by the method described by Chida's group, and tested the orthoamide Overman rearrangement under thermic conditions and also under micro-wave irradiation. Despite numerous experiments, we did not succeed to repeat the reaction to obtain the benzyl substituted derivative **13** (R = Bn) as efficiently as Chida's group, and consequently, we turned our attention to the TBDPS substituted series, otherwise more adapted to the continuation of the total synthesis we have anticipated. The observed isolated yields were slightly higher under microwave conditions (36% compared to 0% with usual heating on a 100 mg-scale), nevertheless disappointing in the scope of a scale-up anticipation (Fig. 4).

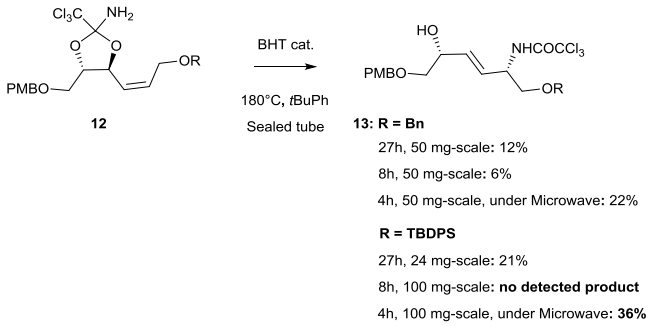

Fig. 4 Orthoamide Overman rearrangement under microwave irradiation.

Supported by the analysis of the samples using ERETIC (Electronic REference To access In vivo Concentrations) NMR method,[38] showing that by-products may exist significantly (estimated to approximately 40%), we have concluded that this approach is not easy at it seemed at first glance. Disappointed by the low yield observed, even after an extensive optimisation, we have decided to carefully think about the orthoamide Overman rearrangement, in order to detect reasons for this rather problematic transformation. In this article, we would like to share with the readers several stereoelectronic introspections into orthoamide diastereoisomers with consequent differential behaviours, in terms of stabilities and reactivities.

A The orthoamide exists as a mixture of two diastereoisomers in equilibrium

The reaction between the precursor diol **14** and trichloroacetonitrile under basic conditions gave two diastereoisomeric orthoamides **12a** (*R*) and **12b** (*S*), in a 1:1 ratio estimated by ^{1}H NMR thanks to nuclear Overhauser effects, separable by HPLC. However reequilibration after standing in solution in $CDCl_3$ at room temperature for 24h has been observed, as already observed by Chida's group on related derivatives (Fig. 5).[4]

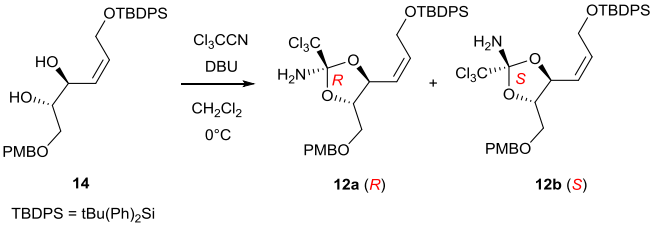

Fig. 5 Two stable diastereoisomers due to the orthoamide formation.

Each diastereoisomer exists as a mixture of conformationally flexible structures, presumably due to the 1,3-dioxolane system,[39] most likely controlled by the semi-equatorial positioning of the bulkier substituent (CCl_3), as exemplified in figure 6, and consequently, conformers **12a-maj** and **12b-maj** should be the major ones.

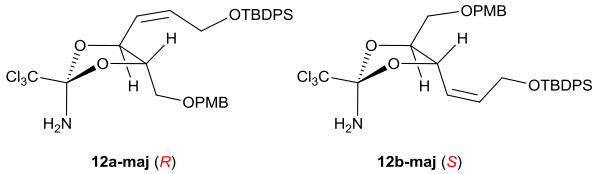

Fig. 6 Major conformers of orthoamide diastereoisomers (**12a-maj** and **12b-maj**).

A first supposed element in the discussion is the possible stabilizing hydrogen bond between NH_2 and OPMB in the case of **12a-maj**, even if this "7-ring" is not very favorable. Consequently, we have anticipated that **12a-maj** may be the most stable diastereoisomer (Fig. 7).

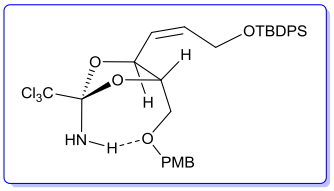

Fig. 7 Stabilising hydrogen bond in **12a-maj**.

B Generation of the trichloroacetimidate 15 from the two orthoamide diastereoisomers

Importantly, during the reaction conditions of Overman rearrangement, each of these diastereoisomers **12a** and **12b** may lead to the crucial intermediate **15**, bearing a trichloroacetimidate on allylic position (Fig. 8). However, this compound may be contaminated by the formation of the unproductive regioisomer **16**, all these species being hypothetically and fortunately in equilibrium.

The difference in behaviours between regioisomer **15** and the "Dead end" regioisomer **16** may be explained by a careful observation of the general figure 1. Indeed, the oxygen moiety should be on allylic position, in order to perform the Overman rearrangement. If for any reason, the equilibrium is difficultly displaced back to the diastereoisomeric orthoamide mixture, and unfortunately favouring the formation of regioisomer **16**, this would be a dramatic sterile dead end for the process. This fact has been previously invocated by Danishefsky, as an insurmountable issue, resulting in failure during one approach in pancratistatin synthesis.[29]

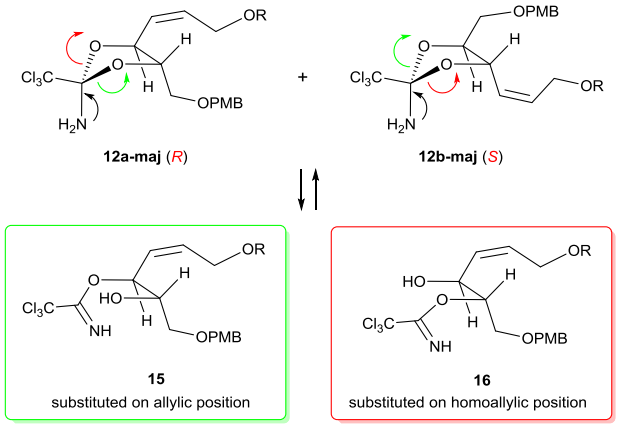

Fig. 8 Equilibrium between conformers of orthoamide diastereoisomers (**12a-maj** and **12b-maj**) and trichloroacetimidate regioisomers.

We believe that all the involved species (**12a**, **12b**, **15** and **16**) deserve complete stereoelectronic and/or modelling studies to understand their behaviours towards a productive Overman rearrangement.

C Stereoelectronic considerations of the different conformers of 12a

In a first step, we only considered the conformational aspects of the 1,3-dioxolane rings and figured out that the necessary subsequent selective opening obeys to stereoelectronic considerations.[40] In a second step, we investigated the different orbital overlaps and for that purpose we drew the most probable staggered conformers, regarding the C-N bond, starting from the possibly most stable **12a** (*R*), named **12a-i**, **12a-ii** and **12a-iii** (Fig. 9).

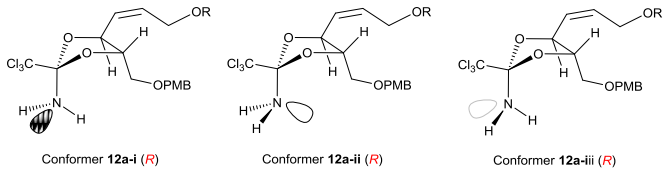

Fig. 9 Most probable staggered conformers of **12a**.

We postulated that the ideal antiperiplanar orbital overlap generates the desired regioisomer **15** (indicated in green in figure 10).

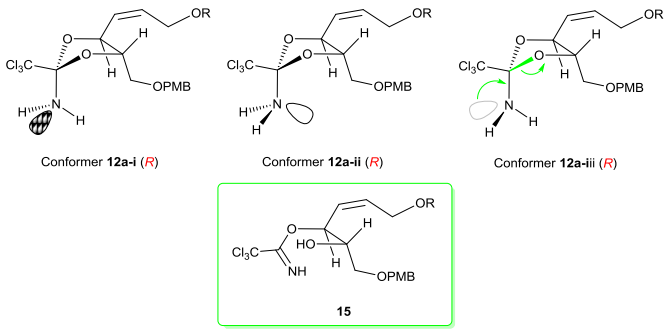

Fig. 10 Only one favorable overlap for most probable staggered conformers of **12a**.

We deduced from the figure 10 that **12a-iii**, satisfying the antiperiplanar overlap, may be the only productive conformer.

D Stereoelectronic considerations of the different conformers of 12b

The same reasoning has been adapted to the most probable staggered conformers, always regarding the C-N bond, for the possibly less stable **12b** (*S*), named **12b-i**, **12b-ii** and **12b-iii** (Fig. 11).

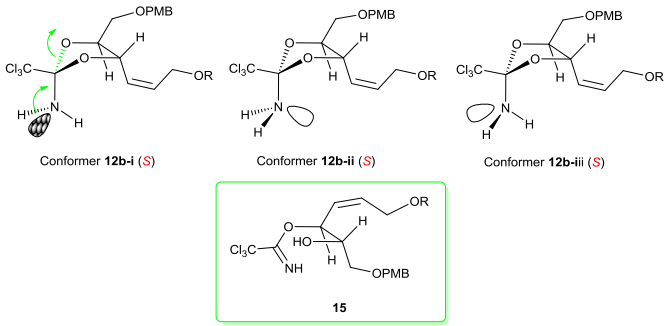

Fig. 11 Only one favorable overlap for most probable staggered conformers of **12b**.

We deduced from the figure 11 that **12b-i**, satisfying the antiperiplanar overlap, may be the only productive conformer.

These first considerations have been completed by molecular modelling studies.

E Molecular modelling studies

The Overman rearrangement is a process involving several transformations (Fig. 12), with all species in equilibrium, each entity existing as many conformers. The hypothesis of our work relies on the supposition that some stable species have the disadvantage not to lead to the desired Overman transformation, which would explain the difficulty of this process.

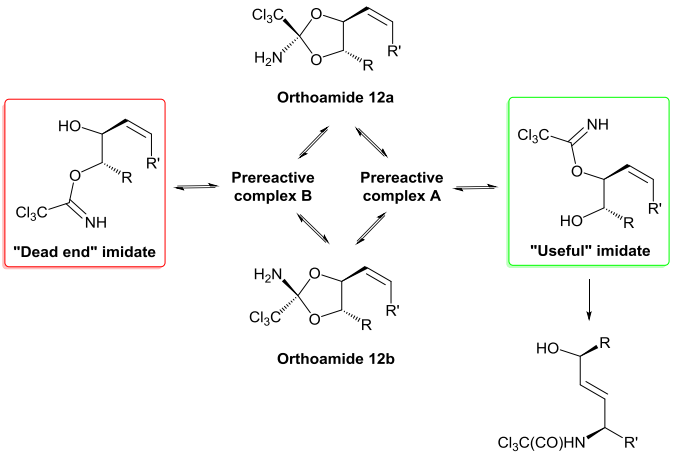

Fig. 12 Species and transformations in the Overman process.

A detailed discussion of the different species, their stabilities and behaviours, underpinned with modelling studies, is described in the

supplementary materials section. The aim of this paragraph is to emphasize the most important points supporting our discussion.

- **Discussion on orthoamides**

The structures and reactivities of orthoamides have been investigated in order to rationalize the difficulty of this Overman rearrangement. To get a quick overview on the conformers of orthoamide diastereoisomers **12a** and **12b**, full geometry optimisations of the six most probable staggered conformers (Fig. 13 and Table 1) have been performed. Even if several molecular conformations have been considered in each case, only results for the most stable ones will be reported here.

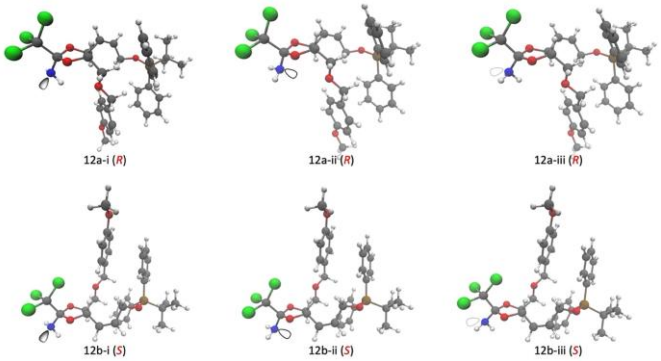

Fig. 13 Optimised structures (wB97X-D/ Def2TZVP level) of the conformers of **12-a** and **12-b**.

Tab. 1. Computed energies at wB97X-D/ Def2TZVP (kcal.mol^{-1}) level and $d_{H(NH2)\cdots O(PMB)}$ in Å

Conformer		ΔE	ΔG			$d_{H(NH2)\cdots O(PMB)}$
			298K	373K	453K	
12a	**i**	0.67	-0.59	-0.88	-1.20	2.890
	ii	0.24	-0.62	-0.81	-1.01	3.798
	iii	1.49	0.95	0.83	0.70	3.518
12b	**i**	2.08	2.10	2.13	2.16	
	ii[1]	0.00	0.00	0.00	0.00	
	iii	2.47	1.91	1.83	1.73	

[1] chosen as reference

A first observation on this table 1 is that the diastereoisomer **12a** (negative values) seems to be a little more stable than the diastereoisomer **12b**. The computed difference of Gibbs free energy is small and sometimes negligible. The smallest values correspond to **12a** at 298K (ΔG ranges from 0.6 to 1 in absolute value) and at 453K (ΔG ranges from 0.7 to 1.2 in absolute value). Nevertheless, this first theoretical consideration shows that **12a-i** and **12a-ii** are the most stable conformers of **12a**. **12b-ii** is the most stable conformer of **12b**. Unfortunately only **12a-iii** and **12b-i** deliver productive imidates (Fig. 10 and 11) whereas these conformers appear to be the most unstable according to Table 1 (even if interconversions between all conformers are clearly very rapid and solve this issue).

In order to justify the stabilities of **12a-i**, **12a-ii** and **12b-ii**, the relatively recent IGM methodology was used.[41-43] This tool is particularly attractive to capture and characterize noncovalent interactions and has shown a weak hydrogen bond in **12a-i** (2.890 Å where usually 2.4-2.5 Å are observed, see ESI).

As an intermediate conclusion regarding the behaviours of orthoamides **12a** and **12b**, *a priori*, the different conformers have differences in energies, to a greater or lesser extent, and could react differently. Importantly, **12a-i**, **12a-ii** and **12b-ii** are the most stable ones, while **12a-iii** and **12b-i** are the most favorable ones for the formation of a useful imidate in the Overman rearrangement (see Fig. 10 and 11), these parameters may slow down the process.

- **Discussion on prereactive complexes**

The possibility of weakening of C-O bonds in the prereactive complex B (Fig. 12) corresponding to the diastereoisomer **12a-i** (presumably giving a "Dead end" imidate, Fig. 8 and 10) was investigated using Intrinsic Reaction Coordinate (IRC) calculations at the wB97X-D/ Def2TZVP level (Fig. 14). This study revealed that one of the C-O bond is weaker (1.406 Å compared to 1.391 Å) with a lower IGM-IBSI index (1.144 compared to 1.196). The prereactive complex B should consequently evolve to cleave this weaker C-O bond, giving the "Dead end" imidate, with the imidate function positioned on an homoallylic position (unproductive for the Overman process).

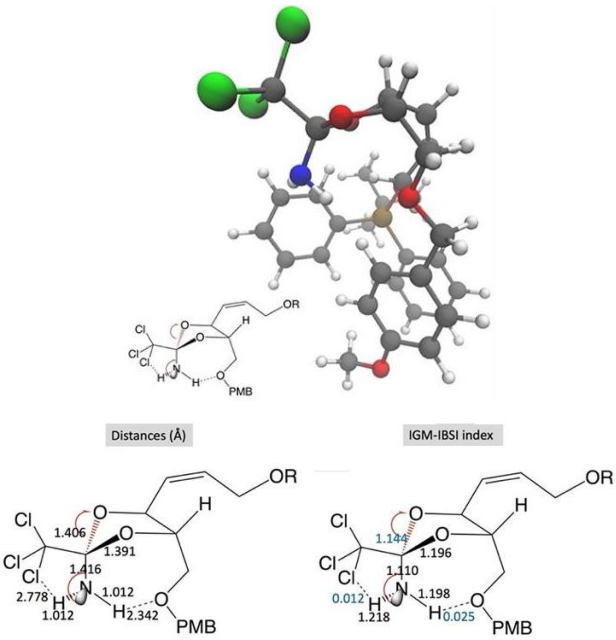

Fig. 14 Prereactive Complex B obtained from the endpoints of IRC calculations at the wB97X-D/ Def2TZVP level for **12a-i**, and schematized structures with bond lengths and IGM-IBSI indexes.

The same approach allowed to study the weakening of C-O bonds in the prereactive complex A (Fig. 12) corresponding to the diastereoisomer **12a-iii** (corresponding this time to the "Useful" imidate), revealing that one of the C-O bonds is weaker (1.404 Å compared to 1.388 Å, see ESI) with a lower IGM-IBSI index (1.156 compared to 1.208). The prereactive complex A should consequently evolve to cleave this weaker C-O bond, giving the "Useful" imidate, with the imidate function positioned on an allylic

place compared to the double bond (productive for the Overman process).

Interestingly, the molecular modelling study indicates that the prereactive complex A resulting from the less stable conformer **12a-iii** is far more stable compared to the prereactive complex B coming from the more stable conformer **12a-i** (Fig. 15). This fact may "confuse" and slow down the overall Overman process.

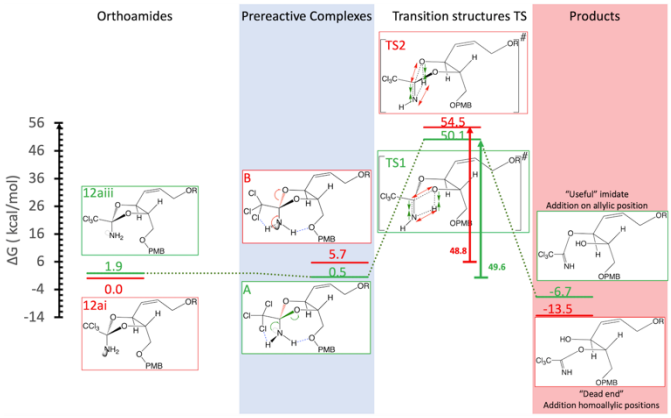

Fig. 15 General reaction mechanism and free energy profile.

Barrier heights for the two possible reactions are calculated to identify the most reactive reaction channels (allylic vs homoallylic positions). The reaction step has a high activation barrier (~50 kcal.mol^{-1}) in the two cases. These (high) Gibbs free energy barriers may explain the requirement of (elevated) temperature in this Overman process and (slow) reaction time.

The addition on allylic position barrier raises (50.1 - 0.5 = 49.6 kcal.mol^{-1}) and the addition on homoallylic position barrier lowers (54.5 - 5.7 = 48.8 kcal.mol^{-1}) but both are similar and high (difference < 1 kcal.mol^{-1} = 0.8 kcal.mol^{-1}). This similarity in barrier indicates that for the addition reaction, there is a competition between addition on allylic position and addition on homoallylic position barrier.

Although the two reactive reaction channels (allylic and homoallylic) are in competition, prereactive complexes show a clear bias for the prereactive complex A corresponding to the "Useful" imidate addition on allylic position (0.5 kcal.mol^{-1} vs 5.7 for the prereactive complex B). Nonetheless, the free energy of the orthoamide conformers (**12a-iii** with the ideal antiperiplanar orbital overlap) is not the lowest one, and the fractional population of this orthoamide conformers is small (5.37 at 453K, 4.22 at 373K, and 2.92 at 298K), which explain the experimental difficulties.

- **Discussion on transition states**

Transition state structures (TS) have been located on the potential energy surfaces at the wB97X-D/ Def2TZVP level using the Gaussian 16 program.[44] IRC analyses have been undertaken to examine the reaction path from the transition state structures of **12a** on a potential energy surface and to check the species connected by a transition state. Satisfyingly, two reactants with a possible stabilizing hydrogen bond between NH_2 and OPMB have been identified from the endpoints of IRC, which is in accordance with our preliminary hypothesis (Fig. 16).

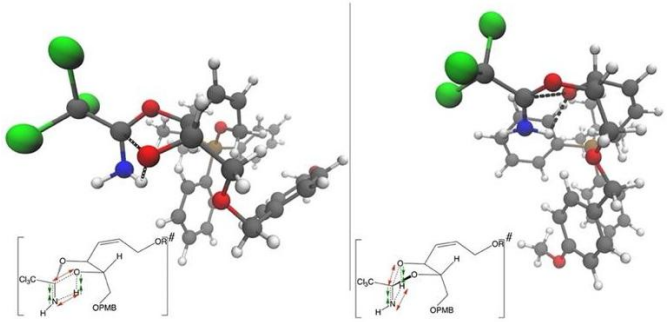

Fig. 16 Transition states structures TS1 (left) and TS2 (right) for **12a** orthoamide diastereoisomer at the wB97X-D/ Def2TZVP level.

The transition state TS1, that leads to the "Useful" imidate on allylic position, has shorter distances for the C-O broken bonds (2.36 Å vs 2.57 Å) and the H-O being formed bonds (1.68 Å vs 1.99 Å) compared to the distances in the transition state TS2, that leads to the "Dead End" imidate on homoallylic position. In the second case (TS2), the C-N distance is shorter (1.29 Å vs 1.33 Å), this one looking like a semi-planar transition state. Some additional computations were also performed to accurately predict the barrier of the two reactions, leading to the imidate product substitutions on allylic and on homoallylic positions. The computed Gibbs free energies for these reactions $\Delta G°‡$ are 49.2 and 54.1 kcal.mol^{-1} for **12a-i** and **12a-iii** respectively. These (high) Gibbs free energy barriers may explain the requirement of elevated temperature in this Overman process.

- **Overall conclusions explaining the problematic formation of imidates in our Overman process**

Overall, several parameters may "confuse" and slow down our Overman process.

Indeed, the different conformers of orthoamides have differences in energies, to a greater or lesser extent, and can react differently. Importantly, **12a-i**, **12a-ii** and **12b-ii** are the most stable ones. In terms of formation of a "Useful" imidate, **12a-iii** and **12b-i** are the most favorable ones.

Additionally, the prereactive complex B resulting from the less stable conformer **12a-iii** is far more stable compared to the prereactive complex A coming from the most stable conformer **12a-i**.

Finally, the computed Gibbs free energies for the reactions $\Delta G°‡$ are equal to 49.2 and 54.1 kcal.mol^{-1} for **12a-iii** and **12a-i** respectively. These (high) Gibbs free energy barriers may explain elevated experimental temperature conditions.

Conclusion

The orthoamide Overman rearrangement is a useful transformation, affording multiply elaborated structures, however suffering from harsh reaction conditions (especially in terms of elevated temperatures). Molecular modelling studies on orthoamides stabilities and transition states evolutions buttress these observations and we believe that

stereoelectronic effects may explain the reasons of these difficulties. The requirement of a specific steric arrangement allows to thread the way into the desired product. We hope this study will contribute to help the readers to understand their results, anticipating transformations for better processes.

Author Contributions

Judith Juvin: Investigation and Writing – Review and Editing; Victor Malherbe: Investigation; Marie-Charlotte Belhomme: Conceptualization and Writing – Review and Editing; Stéphanie Castex: Formal analysis, Resources and Writing – Review and Editing; Hassan Khartabil: Molecular modelling and Writing; Agathe Martinez: ERETIC (Electronic REference To access In vivo Concentrations) NMR measurements; Arnaud Haudrechy : Methodology, Project administration, Supervision and Writing.

Conflicts of interest

There are no conflicts to declare.

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