Results in Chemistry 5 (2023) 100820

Contents lists available at ScienceDirect

Results in Chemistry

journal homepage: www.sciencedirect.com/journal/results-in-chemistry

From optically pure pyridinium salts to some new dihydro-2H-oxazolo [3,2-*a*]pyridines

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ARTICLE INFO

Keywords:
Chiral Katritzky salts
Oxazolo[3,2*a*]pyridines
Isoquinuclidine

ABSTRACT

Treatment of 2,4,6-triphenylpiridinium salts, bearing a chiral β-hydroxy alkyl *N*-substituent with diluted aqueous sodium hydroxide afforded four new dihydrooxazolo[3,2*a*]pyridines,as an almost equimolar mixture of diastereomers. However, a highly selective ring closure reaction was observed for the pyridium salt derived from (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol.

Introduction

Enantiopure β -hydroxythiols have found application in the preparation of biologically active compounds as, for example, selective inhibitors of matrix metalloproteinases [1], antitumor agents [2], and thiol androgen acting as human placental aromatase inhibitors [3]. Despite their importance as synthetic building blocks, the preparation of β -hydroxythiols relies almost exclusively on the ring opening of some readily available chiral [1] or *meso*-epoxides. In the latter case, the dissimetrization [4] is accomplished either by the intervenience of metal chiral complexes [5–7] or organocatalysts [8,9]. An alternative asymmetric approach as applied to the synthesis of tertiary thiols in up to 97 % enantiomeric excess was based on the intramolecular sulfur transfer in *N*-enoyl oxazolidine-2-thiones promoted by a Lewis acid, during sulfa-Michael reactions [10,11]. In an ongoing project of our laboratory, we became interested in some β -hydroxythiols as potential ligands for gold nanoparticles. As for the synthesis of these compounds, we envisaged that 2,4,6-pyridinium tetrafluoroborates bearing a chiral *N*-substituent could be convenient and easily prepared starting materials.

The 2,4,6-triphenylpyridinium salts (Katritzky salts) have recently found new synthetic applications, mainly in the field of catalyzed or uncatalyzed visible light-induced processes [12]. However, the ionic reactions of these salts are still to be considered for transforming amines into other functionalities [13], including stereoselective reactions [14]. In a search for a suitable method for the preparation of enantiopure β -hydroxythiols from 2,4,6-triphenylpyridinium tetrafluoroborates bearing a chiral hydroxylated *N*-substituent, we decided to perform the substitution reaction on *N*-alkyl-2,4,6-triphenyl-pyridinium tetrafluoroborates, using potassium thiobenzoate as an external nucleophile and dioxane or toluene as the solvent under reflux [15]. Thus, the resulting chiral thioesters would be suitable precursors of the desired β-hydroxythiols by a simple acid hydrolysis procedure.

The starting pyridinium salts were prepared by reacting the 2,4,6-triphenylpyrilium tetrafluoroborate with four configurationally-defined aminoalcohols. The expected products were obtained in reasonable yields (50 %-65 %) and were fully characterized (Scheme 1).

As for the ionic displacement reactions, heating of a mixture of salts **1** or **2** and potassium thiobenzoate, in toluene under reflux, yielded the expected thioesters **5** and **6**, in 10 % and 50 % yield, respectively, after separation from the liberated 2,4,6-triphenylpyridine by column chromatography on silica gel (Scheme 2). However, upon applying the same procedure to salts **3** and **4**, the ^{1}H NMR spectra of both crude products showed an intense resonance signal due to aldehydic protons. Such aldehyde formation was previously reported for the thermolysis of some analogous *N*-hydroxy-alkyl pyridinium salts [16].

The optical purity of the thioester derived from pyridinium **1** was investigated and could be confirmed via the ^{1}H NMR spectra, in the presence of the chiral shift reagent Europium tris[(3-heptafluoropropylhydroxymethylene)-(+)-camphorate] (Fig. 1). This experimental evidence excluded the occurrence of racemization at any of the two preparation steps.

Although pyridinium salts **1**–**4** seemed to be of limited use for the preparation of chiral thioesters, a new application of such compounds as precursors of chiral dienes can be envisaged. In fact, upon treatment of pyridinium **1**–**4** with a diluted solution of aqueous sodium hydroxide, they were readily transformed into the corresponding dihydrooxazolo [3,2-*a*]pyridines **7**–**10** in good yields, by direct attack of the deprotonated hydroxyl group to the C-2 or C-6 ring carbons. This kind of

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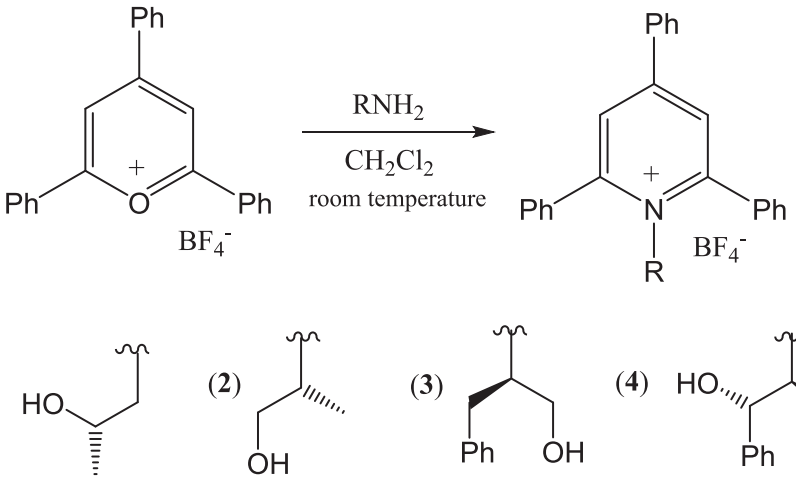
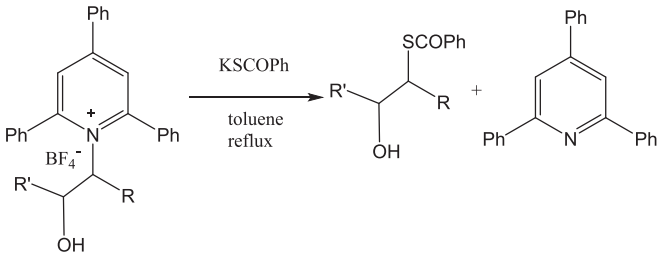
https://doi.org/10.1016/j.rechem.2023.100820
Received 19 January 2023; Accepted 30 January 2023
Available online 1 February 2023



Scheme 1.



(**1**) R = H, R' = CH_3
(**2**) R=CH_3, R'= H

(**5**) R = H, R' = CH_3
(**6**) R=CH_3, R'= H

Scheme 2.

transformation was previously reported for some racemic 2,4-diphenyl pyridinium ethanols, but no spectroscopic data were presented due to poor stability of products [17]. In fact, in the presence of even traces of acid, the newly synthesized 1,2-dihydropyridines are partially transformed back to the pyridinium salts. In our case, the diastereomeric ratios of the crude products were estimated directly from their ^{1}H NMR spectra, being c.a. 1:1, except for the 1,2-dihydropyridine derived from pyridinium **4** (Table 1).

Aiming to access the structure of the major diastereomer of the oxazolidine derived from pyridinium salt **4**, the diastereomeric mixture was submitted to the 1,4-cycloaddition reaction with *N*-methylmaleimide.

Surprisingly, only one Diels-Alder adduct was formed, in 93 % yield, as determined from the ^{1}H NMR spectrum of the crude product, using dibenzylether as an internal standard. This result points to the preferential attack to one face of the dihydropyridines **10 or 10′** as well to the isomerization of the minor diastereomer.

^{1}H NMR and ^{13}C NMR experiments (HSQC, HMBC and NOESY) allowed for the assignment of the structure of Diels-Alder adduct **11,** prepared by reacting oxazolidine **10** and *N*-methylmaleimide (Fig. 2).

However, considering the *N*-maleimide attachment to any of the two different faces of the coexisting diastereomers of oxazolidine **10**, four different adducts could be formed (Fig. 3).

In order to understand the origin of the observed selectivity and to deeper investigate the pathways of the reaction between **10** and the *N*-methylmaleimide, some theoretical calculations were performed at the DFT framework (see Supporting Information for details).

The energies of the transitions states (TSs), intermediates (IMs), and adducts were estimated, as shown in Fig. 4, being the relative energies of all minima and TSs presented in terms of free energies in kcal/mol with respect to the infinitely separated reactants. From the calculated energies, it can be concluded that adduct **D** is kinetic and

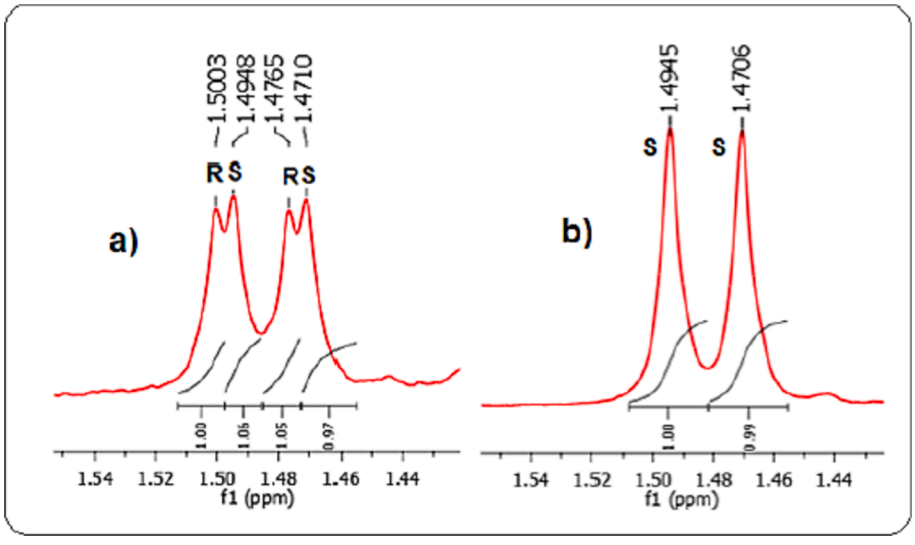
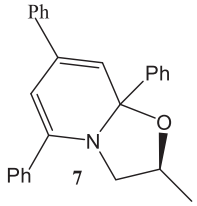
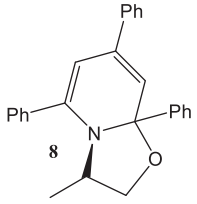
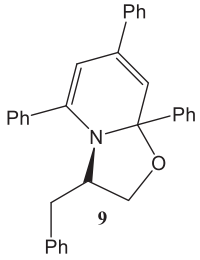
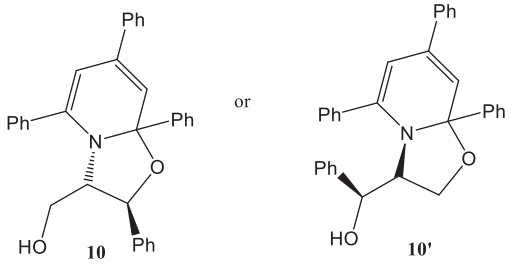


Fig. 1. ^{1}H NMR spectra in the presence of Eu(hfc)$_3$ a) racemic **5** b) product of nucleophilic displacement reaction on pyridinium **1.**

Table 1
Dihydrooxazolo[3,2-*a*]pyridines **5**–**8** from pyridinium salts **1**–**4.**

Pyridinium salt	Oxazolidine	Yield(%)	Diastereomeric ratio
1		86	1:1.2
2		90	1 : 1.4
3		64	1 : 1.2
4		94	1 : 10

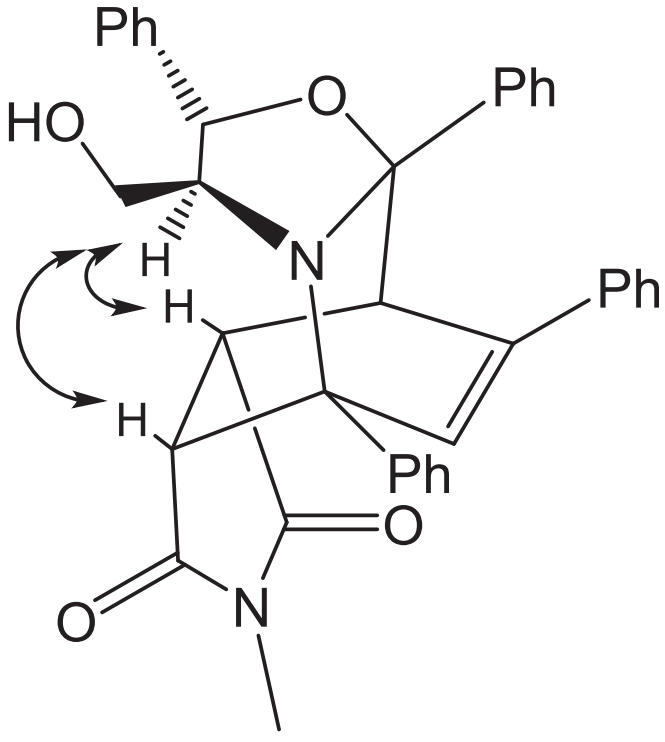


Fig. 2. Structure of *endo* adduct **11**.

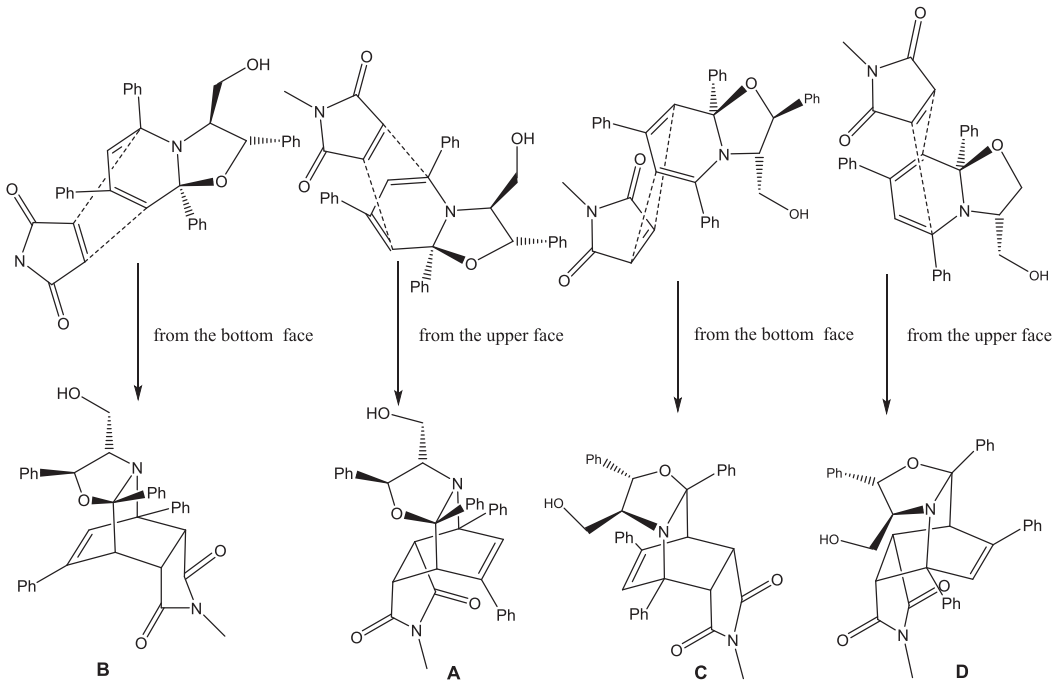


Fig. 3. Structure of *endo* adducts **11.**

thermodynamically favored. However, adduct **D** is only slightly more stable than adduct **C**, as their energy difference is only 0.8 kcal mol^{-1}. On the other hand, the TS energy barrier for the formation of adduct **C** is 7.9 kcal mol^{-1} greater than that for adduct **D**. As for the two other possible adducts (**A** and **B**), they are much less stable in comparison to **C** and **D**. Adducts **B** and **C** have the higher TS energies as compared to **A** and **D**, suggesting that the dienophile approaches preferentially to the upper face of the diene. In view of this panorama and to better understand the observed selectivity, non-covalent interactions (NCI) analyses were carried out, searching for the existence of hydrogen bonds, van der Waals (vdW) and repulsive and attractive interactions that would be responsible for the stabilization of the TSs and resulting adducts.

The (NCI) analysis provided a 3D representation, namely NCI isosurfaces of the spatial interactions according to a RGB color scale, where red stands for repulsive, green for van der Waals, and blue for attractive interactions. Based on the NCI isosurface analysis, the TS of adduct **D** is stabilized by C—H···π, OH··· π and C—H···O hydrogen bond interactions, as shown in Fig. 5. These interactions are represented as a

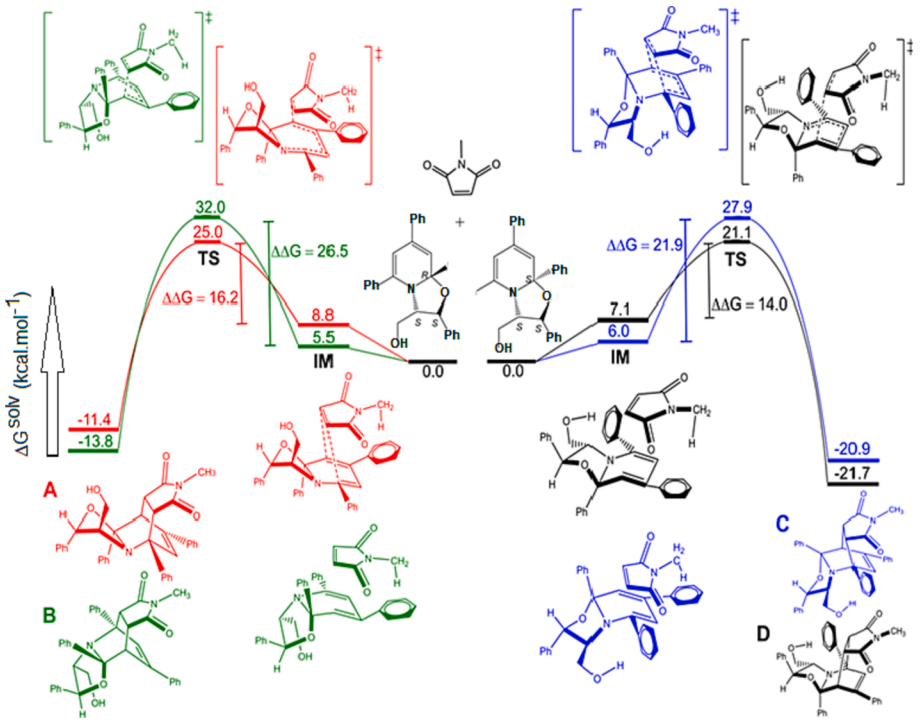


Fig. 4. Reaction pathways for the formation of the Diels-Alder adducts for the cycloaddition reaction between **10** and *N*-methylmaleimide at the M06-2X/cc-pVDZ level of theory.

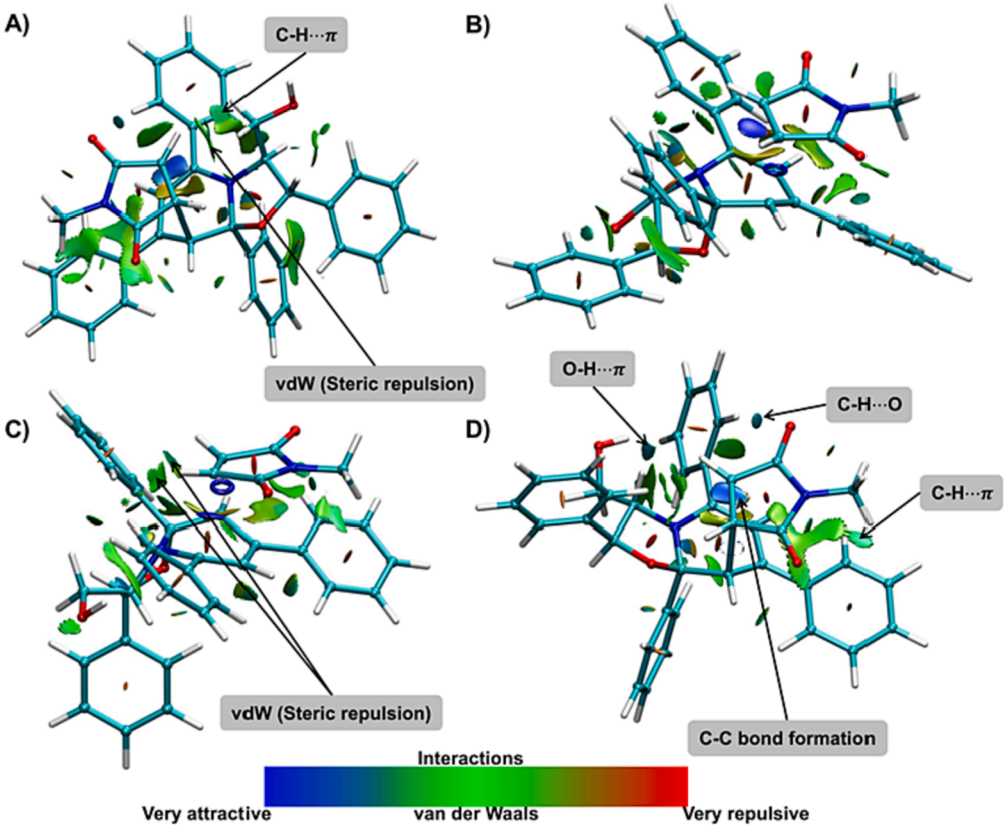


Fig. 5. Non-covalent interactions (NCI) isosurfaces for the transition states of the reaction pathways between *N*-methylmaleimide and dihydropyridine **10** obtained at the M06-2X/cc-pVDZ level of theory. The attractive, van der Waals (vdW), and repulsive interactions are defined by s = 0.03 a.u. and a blue-green–red color scale from −0.03 < sign(λ2)ρ < 0.03 a.u. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

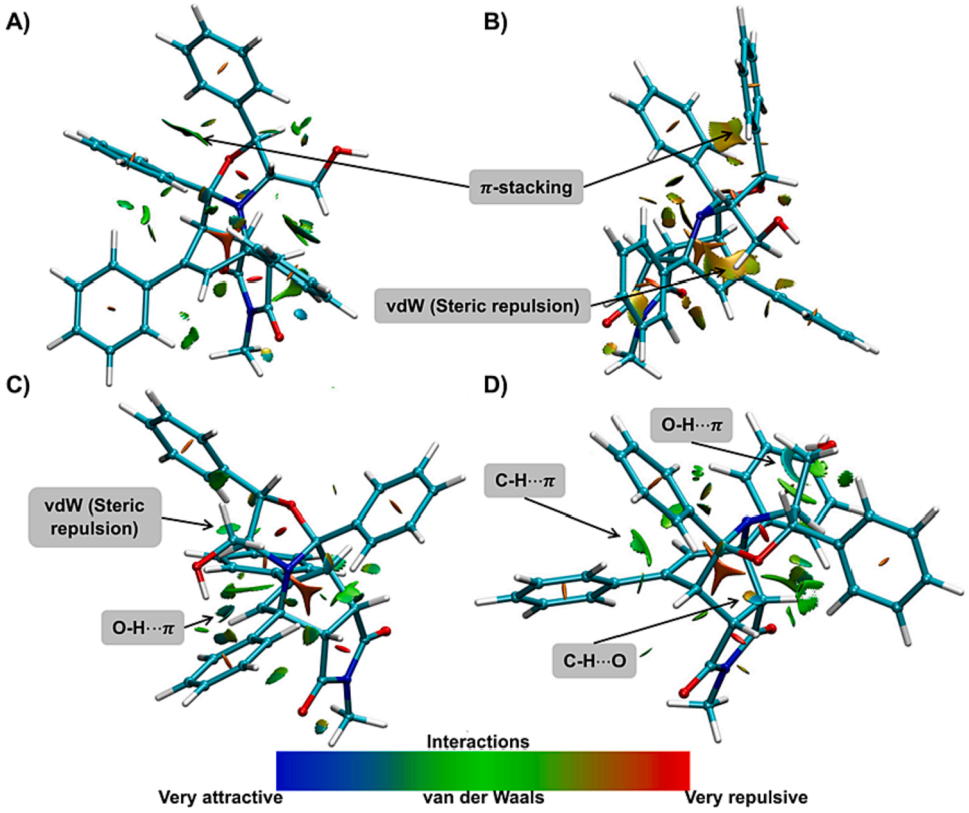


Fig. 6. Non-covalent interactions (NCI) isosurfaces for the adducts of the reaction pathways between *N*-methylmaleimide and dihydropyridine **10** obtained at the M06-2X/cc-pVDZ level of theory. The attractive, van der Waals, and repulsive interactions are defined by *s* = 0.03 a.u. and a blue-green–red color scale from −0.03 < sign $(\lambda_2)\rho$ < 0.03 a.u. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

blue-green gradation in the dispersion domain characteristic of the dispersive interaction. The red regions located at the center of each ring are non-bonded overlap, representing the expected steric repulsion between the carbons of each ring. The TS of **C** presents similar interactions to the ones observed in **D**, except for the absence of a CH···O bond. However, there is an extra repulsive interaction between the phenyl groups of the 1,2-dihydropyridine and the *N*-methylmaleimide, restraining the approximation of the reactants, and leading to a higher TS energy barrier than found for the TS of **D**. Analogously, in TS of **A** there is a repulsive interaction between the approaching maleimide and the CH_2OH group of the 1,2-dihydropyridine. The smaller size of the CH_2OH group, as compared to a phenyl group, accounts for a smaller energy barrier for TS of **A** as compared to TS of **C**. Additionally, in TS of **A,** there is also an intramolecular attractive interaction between the same CH_2OH group and one of the three phenyl groups of the dihydropyridine molecular structure. Overall, adduct **A** is slightly kinetically favored compared to adduct **C**.

As depicted in Fig. 5, TS of **B** has a strongly sterically hindered structure due to repulsive interactions between the maleimide and both phenyl groups of the 1,2-dihydropyridine. Additionally, the absence of any stabilizing interaction, accounts for the highest calculated energy barrier.

Regarding the reaction products (Fig. 6), adduct **D** is slightly more stable than adduct **C** by only 0.8 $kcal{\cdot}mol^{-1}$. According to the NCI analysis, such difference can be attributed to the spatial interaction between phenyl groups through CH···π, leading to extra stabilization. On the contrary, in adduct **C,** the phenyl groups interact repulsively. Additionally, a CH···O interaction is observed for adduct **D**.

In adducts **A** and **B**, a π-stacking interaction between phenyl groups could be identified, contributing to their stabilization. However, in both adducts there is a steric repulsion between the CH_2OH and the phenyl groups at the isoquinuclidine ring junction. Considering all four adducts, there are fewer stabilizing interactions in adducts **A** and **B,** as compared to **C** and **D,** accounting for the overall calculated stability order.

Conclusion

In conclusion, four pyridinium tetrafluoroborates, bearing a configurationally-defined *N*-substituent, were prepared and readily transformed into novel 1,2-dihydropyridines that are useful precursors of the quinuclidine structural skeleton.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

We are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for scholarship to one of us, to Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)(2018-15343-4; 2018/07308-4) and to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2023.100820.

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