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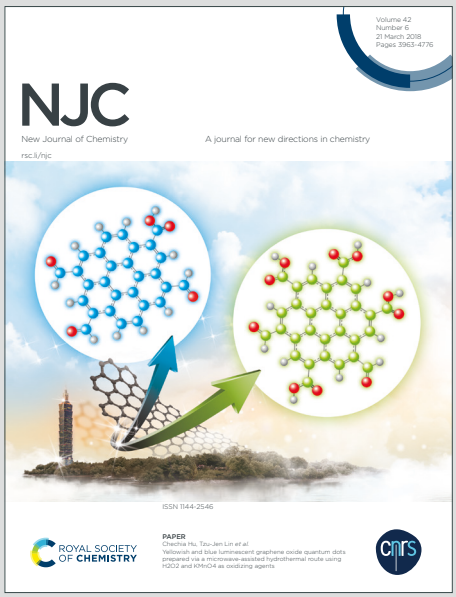

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ARTICLE

Synthesis and X-ray crystallographic analysis of free base and hexafluorophosphate salts of 3,4-dihydroisoquinolines from the Bischler-Napieralski reaction

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The Bischler-Napieralski reaction of *N*-phenylethyl cinnamamides was investigated in acetonitrile and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6). Strong effects on the nature of the isolated products were observed depending on the structure of the starting materials and the solvent used. The corresponding 3,4-dihydroisoquinoline as a free base was isolated when acetonitrile was employed, but the respective 3,4-dihydroisoquinolines, as hexafluorophosphate salts, were obtained when [bmim]PF_6 was used as a reaction media due to an anion methatesis between the reaction intermediates and the solvent. A full X-ray crystallographic analysis for a 1-phenethyl-3,4-dihydroisoquinoline derivative is reported for the first time and revealed that in this core, as a free base, the torsion angle C10-N1-C9-C8 allows the existence of two conformers, crystallizing in a centrosymmetryc $P2_1/n$ space group. However, only one conformer crystallized in the hexafluorophosphate salt, therefore describing an enantiomorphic $P6_1$ space group. The absence of type II symmetry operations allowed the formation of 1D-channels that contain the PF_6-anions and cross the entire structure along [001] direction giving interesting potential uses as ionic conductor. Additionally, CE-B3LYP model energies showed that in both crystal structures, dispersion forces have an important role in the supramolecular architecture. Nevertheless, in the hexafluorophosphate salt electrostatic forces increase the structural stability to a total packing energy of -173.6 kJ/mol, compared with the free base with a value of -135.0 kJ/mol.

1. Introduction

One of the largest family of naturally occurring alkaloids are the nitrogen-containing heterocycles with the isoquinoline core.[1] Nowadays, these natural and synthetic derivatives are recognized for their broad range of pharmacological activities,[2] and among them, the C1- substituted 3,4-dihydroisoquinolines such as: Nelumstemine **1**,[3] Longifolonine **2**,[3,4] Velucryptine **3**,[5] and the tetrahydroisoquinolines: Noscapine **4**,[6] Dysoxyline **5**,[7] and Cryptostiline I **6**[8] that represent an important and promising group of analogues with diuretic, astringent, cardiac, antiviral and anticancer activities (Figure 1).

Currently, for the synthesis of 3,4-dihydroisoquinolines a series of interesting protocols, such as Pictet-Spengler[9] and Pomeranz-Fritsch[10] strategies have been well developed, but the Bischler-Napieralski reaction has been one of the preferred methodologies due to its practicability and reliability for accessing the 3,4-dihydroisoquinoline core.[11] This has been a well-studied reaction in organic chemistry, where *N*-arylethyl amides bearing electron-rich arenes are well tolerated as substrates, and $POCl_3$, PCl_5 or P_2O_5 can be used as dehydrating reagents, while the reaction can be carry on in CH_3CN, toluene or CH_2Cl_2 as a solvent or under free-solvent conditions at different temperatures (40-100 °C).[12,13] In the special cases in

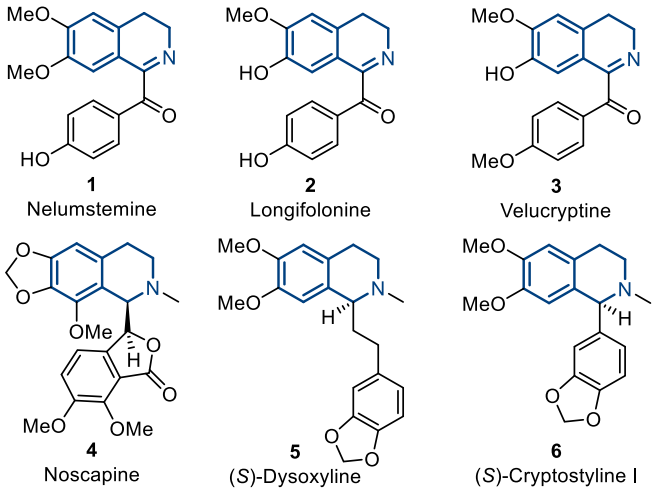

Fig 1. Representative bioactive 3,4-dihydro- and tetrahydroisoquinolines (**1**-**6**).

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which *N*-phenylethyl cinnamamides are employed as substrates for the synthesis of 1-styryl-3,4-dihydroisoquinolines, Cortes *et al.* reported previously that intermediates with the 1-styryl-3,4-dihydroisoquinoline core were unstable and these authors choose to transform these derivatives instead of study their isolation.[14]

Recently, we established an efficient protocol for the synthesis and isolation of a series of 1-styryl-3,4-dihydroisoquinolines as hexafluorophosphate salts in excellent yields[15], in contrast to the previous methodology reported by McCluskey *et al.* who obtained simple 3,4-dihydroisoquinolines derivatives as a free bases.[16] The isolation of isoquinolinium salts is relevant from the pharmacological point of view, in order to increase oral biodisponibility (absortion), aqueous solubility (blood transport) and stability,[17] or for chemical purposes such as facilitate the asymmetric hydrogenation of isoquinolines.[18] Therefore, it is highly desirable to obtain these derivatives in one step instead of the current protocols, which isolate the respective isoquinolines and then treat them in an additional step with organic or inorganic acids to obtain the corresponding salts.

Thus, considering the interest in exploring the chemistry of 3,4-dihydroisoquinolines, we envisioned that manipulating the structure of the starting materials and the reaction conditions, specially the solvent and temperature of the Bischler-Napieralski reaction, we could obtain 3,4-dihydroisoquinolines of great interest, as free bases or PF_6-salts, crystalize them, confirm their structure by single crystal X-ray diffraction analysis and perform computational calculations at B3LYP level of theory to explore their supramolecular characteristics in solid state and stability regarding the PF_6-anion.

2. Experimental

2.1 Synthesis

A general procedure and the characterization data of compounds are shown in supporting information.

2.2 Refinement and computational methods

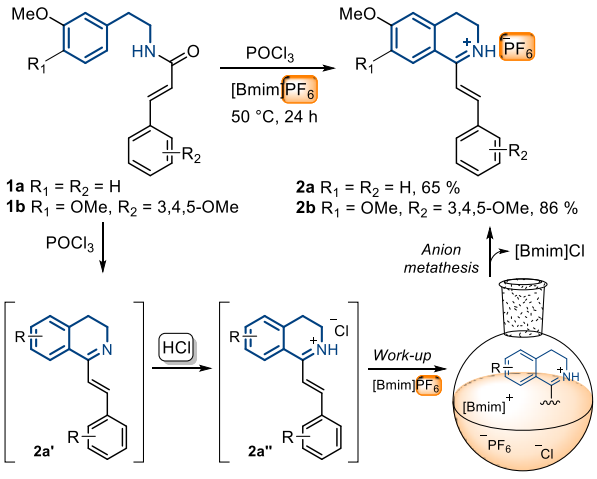
The X-ray intensity data were measured at room temperature [298 (2) K] using Mo*Kα* radiation (λ = 0.71073 Å), and ω scans, in an Agilent SuperNKova, Dual, Cu at Zero, Atlas four-circle diffractometer equipped with a CCD plate detector. The collected frames were integrated with the CrysAlis PRO software package (*CrysAlisPro 1.171.39.46e, Rigaku Oxford Diffraction, 2018*). Data were corrected for the absorption effect using the CrysAlis PRO software package by the empirical absorption correction using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm. All the non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were generated geometrically, placed in calculated positions (C–H = 0.93–0.97 Å; N–H = 0.86 Å), and included as riding contributions with isotropic displacement parameters set at 1.2–1.5 times the U_{eq} value of the parent atom. The crystal structures were refined using the program SHELXL2014.[19] Molecular and supramolecular graphics were carried out using the software Mercury.[20] In order to obtain a better understanding of the crystal packing, the crystallographic analysis was complemented with calculations using CE-B3LYP energy model based on B3LYP/6-31G(d,p) quantum mechanical charge distribution for unperturbed monomers which was applied to the molecular crystals. This model is implemented in CrystalExplorer. In these calculations, the total interaction energy was modeled as the sum of the electrostatic (E_{ele}), polarization (E_{pol}), dispersion (E_{dis}), and exchange–repulsion (E_{rep}) terms based on molecular wavefunctions calculated applying the crystal symmetry obtained from X-ray crystallographic results.[21,22,23] Hirshfeld surfaces (HFs) mapped over d_{norm} were calculated using TONTO, a Fortran-based object-oriented system for quantum chemistry and crystallography, by the B3LYP method using the 6-31G(d,p) basis set implemented in CrystalExplorer.[24]

3. Results and discussion

3.1 Synthesis

We began our study performing the synthesis of the respective 1-styryl-3,4-dihydroisoquinolin hexafluorophosfates **2a-b** through the Bischler-Napieralski reaction starting from the *N*-phenethyl cinnamamides **1a-b** and employing the ionic liquid [bmim]PF_6 as a solvent accordingly to our previous report (Scheme 1).[15]

In this stage, the reaction proceeded smoothly to form the corresponding 1-styryl-3,4-dihydroisoquinoline **2a'**, which immediately reacted with the HCl released from the Bischler-Napieralski reaction to furnish the respective hydrochloride **2a''** (Scheme 1). The excess of $POCl_3$ used also increases the concentration of HCl (pK_a = -5.9) in the reaction media, and when the reaction was treated with crushed ice during the work-up, an aqueous solution is formed in which two cations ([bmim]$^+$ and dihydroisoquinolinium) and two anions (Cl^- and PF_6^-) are present and interacting. At this point, an anion metathesis occurs, in which the chlorine anion affects the



Scheme 1. Anion metathesis promoted by the ionic liquid [bmim]PF_6 during the synthesis of dihydroisoquinoline-hexafluorophosfates **2a-b**.

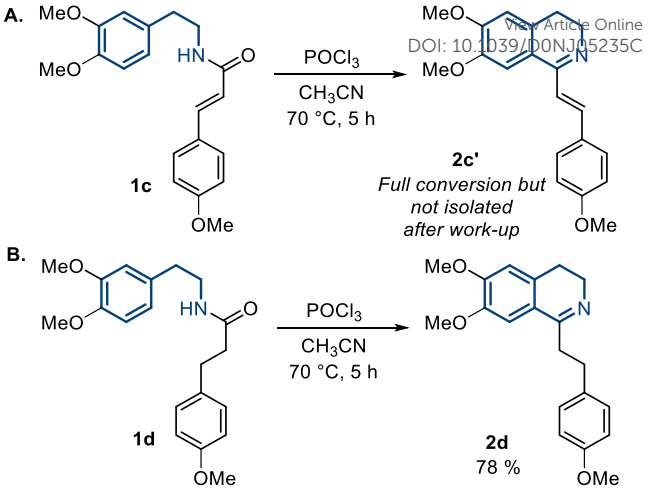
[bmim]$^+$ environment and displaces the PF_6^- anion to form the more stable ionic liquid [bmim]Cl and HPF_6 (pK_a = -10), since the interactions between [bmim]$^+$ and the Cl^- are stronger than with the PF_6^- anion.[25] Finally, in a parallel process, the dihydroisoquinolinium cation reacted with HPF_6 to form an insoluble product that precipitated as hexafluorophosfate salts **2a-b**, which were then recrystallized from a mixture of ethanol an ethyl acetate in a 5:2 ratio at room temperature (Scheme 1). In particular, compound **2a** resulted to be partially soluble in $CDCl_3$, and for practicity, during its characterization through NMR spectroscopy, small drops of non-deuterated ethanol were added to improve its solubility and analysis by this technique (Please see ESI).

Then, we focused our efforts in exploring the synthesis and isolation of the intermediate **2a'**. In first place, we found that when substrate **1a** was subjected to the most common reaction conditions of the classical Bischler-Napieralski reaction, using 8 equiv. of $POCl_3$, toluene as a solvent and warming the reaction at 100°C for 3 hours, the full conversion of the cinnamamide **1a** was achieved. But unfortunately, during the purification process of the obtained product by routine physical methods, we noticed that this compound rapidly decomposed and it could not be well manipulated and stored under standard laboratory conditions.

With the hypothesis that including more methoxy groups as substituents on both aromatic rings of the starting cinnamamide would increase the stability of the desired 3,4-dihydroisoquinoline, we evaluated the respective *N*-(3,4-dimethoxyphenylethyl)-4-methoxycinnamamide **1c** as a substrate of the Bischler-Napieralski reaction under the common reaction conditions (Scheme 2A). Although the full conversion of this substrate was determined by TLC, once again, any attempt to isolate the desired 1-styryl-3,4-dihydroisoquinoline **2c'** as a free base failed.

Clearly, the conjugated C=C-C=N system of the dihydroisoquinoline core in the respective intermediate **2c'** affected the stability of these compounds, inducing their degradation under aerobic, basic or neutral conditions, as was evidenced when we tried their purification by column chromatography using silica gel or alumina as stationary phase. In this sense, we established that 1-styryl-3,4-dihydroisoquinolines could be stable only under acidic conditions and that they could only be isolated as PF_6-salts, where the use of [bmim]PF_6 as a solvent induced the discussed anion metathesis and stabilized these derivatives as hexafluorophosfates instead of hydrochlorides.

Being aware of the negative effect that the α,β-unsaturation in compounds **1a-c** induced on the stability of the expected products **2a'-c'**, and that recently Chen *et al.* also reviewed in specialized literature that during the total synthesis of some tetrahydroisoquinoline alkaloids the preferred starting materials were substrates without the conjugated C=C-C=N system,[26] we focused our efforts in preparing the stable 1-phenethyl-3,4-dihydroisoquinoline **2d** analogue from *N*-phenethylpropanamide **1d** (Scheme 2B). Compound **2d** was readily synthetized using 8 equiv. of $POCl_3$, acetonitrile as a solvent at 70 °C for 6 h in 78 % yield, but the very delightful



Scheme 2. Attempts in preparing the 3,4-dihydroisoquinoline core as a free-base in acetonitrile. A) starting from cinnamamide **1c**; B) starting from propanamide **1d**.

results were that we could isolate this derivative as a free-base and as a solid which was crystalized from ethanol. To the best of our knowledge, this is the first time that a 1-phenethyl-3,4-dihydroisoquinoline of this nature is isolated as a solid instead of an oil or a gummy product difficult to handle (Scheme 2B).

3.2 Crystal structure description

Crystal data, data collection and structure refinement details are summarized in Table 1.

Single crystals of 1-styryl-3,4-dihydroisoquinolin hexafluorophosfates **2a-b** were obtained from a mixture of ethanol and ethyl acetate in a 5:2 ratio at room temperature, while 1-phenethyl-3,4-dihydroisoquinoline **2d** was recrystallized from ethanol. These molecules were studied in their solid states and their molecular structures are shown in Figure 2.

Single crystal X-ray analyses revealed that **2a** and **2d** crystallize in the Hexagonal $P6_1$, and Monoclinic $P2_1/n$ space groups, respectively. While **2d** forms a centrosymmetric crystal structure, **2a** crystallizes in an enantiomorphic space group. This last behaviour contrasts with the centrosymmetric structure observed in 3,4-dihydroisoquinoline-hexafluorophosphate **2b** with a Triclinic *P*-1 space group (Table 1).[15] This difference is due to a conformational effect mediated by changes over the C10-N1-C9-C8 torsion angle (**2a**/**2d** numbering) as shown in Figure 3.

In the case of compounds **2b** and **2d** (Figures 3B and 3C), these conformations are not superimposable. In the case of compound **2a**, only one conformer crystallizes forming an enantiomorphic structure (Figure 3A).

According to the search in the CSD database version 5.41 (November 2019 with 2 updates, May 2020) through the ConQuest software version 2020.1.1 for molecules with the same core, only two related crystal structures are reported so far: the 3,4-dihydroisoquinoline-hexafluorophosphate[15] **2b** and the methanol-solvate 6,7-dimethoxy-2-[(4-

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Table 1. Crystal data and structure refinement parameters for **2a-b** and **2d**

	2a	**2b**	**2d**
Crystal data			
Chemical formula	$C_{18}H_{18}NO{\cdot}F_6P$	$C_{22}H_{26}NO_5{\cdot}F_6P$	$C_{20}H_{23}NO_3$
M_r	409.30	529.41	325.39
Crystal system, space group	Hexagonal, $P6_1$	Triclinic, P-1	Monoclinic, $P2_1/n$
Temperature (K)	298(2)	298(2)	298(2)
a, b, c (Å)	9.8217 (9), 9.8217 (9), 32.600 (5)	8.3124 (9), 11.6899 (11), 12.2686 (8)	11.8343 (16), 12.4529 (11), 14.8774 (18)
α, β, γ (°)	90, 90, 90	78.204 (7), 88.640 (7), 84.652 (8)	90, 106.205 (13), 90
V (Å^3)	2723.4 (7)	1161.88 (19)	2105.4 (4)
Z	6	2	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.22	0.20	0.07
Data collection			
Diffractometer	SuperNova, Dual, Cu at zero, Atlas		
Absorption correction	*Multi-scan (CrysAlis PRO; Agilent, 2014)*		
T_{min}, T_{max}	0.369, 1.000	0.709, 1.000	0.882, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	32276, 4016, 3153	25972, 5125, 3963	24600, 4619, 3110
R_{int}	0.087	0.048	0.050
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.641	0.641	0.641
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.064, 0.187, 1.07	0.058, 0.174, 1.07	0.085, 0.264, 1.76
No. of reflections	4016	5125	4619
No. of parameters	300	388	221
H-atom treatment	H-atom parameters constrained	H-atoms treated by a mixture of independent and constrained refinement	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.32, −0.26	0.44, −0.43	0.50, −0.40
Absolute structure	Flack x determined using 1212 quotients[27]	---	---
Absolute structure parameter	0.05 (7)	---	---

methylphenyl)sulfonyl]-1-[2-(4-nitrophenyl)ethenyl]-1,2,3,4-tetrahydroisoquinoline, which crystallizes in the enantiomorphic $P2_12_12_1$ space group.[28]

For **2a**, a combination of strong N1–H1D···F5^{i}, C12–H12···F3^{i} and C1–H1B···F4^{ii} (symmetry codes: (i) y,1-x+y,-1/6+z; (ii) 1+x,1+y,z) hydrogen bonds join molecules forming a molecular helix wrapped around *c* axis (Table 2 and Figure 4), which is a consequence of the 6-fold screw axis with direction [001] and screw component [0 0 1/6]. These short interactions have H···F distances of 2.14 Å, 2.48 Å, and 2.18 Å, respectively. Between neighbouring spirals, the fluorophosphate ions act as linkers with weak interactions C6–H6···F6, C15–H15···F1, and N1–H1D···F2 with H···F distances of ~2.65 Å (Figure 4).

The fluorophosphate groups are contained in [001] channels occupying the 20.6 % of the crystalline space which corresponds to a volume of 560.4 Å^3 in the unit cell. This value was calculated assuming a molecular contact surface, that is, the walls of the channels directly in contact with the surrounding molecules (Figure 5A). The formation of these channels is a consequence of the absence of inversion centers due to the presence of only one conformer which allows the building of the spiral-like crystal structure (Figure 5A).

When the space occupied by the fluorophosphate groups is calculated in the related 3,4-dihydroisoquinoline-

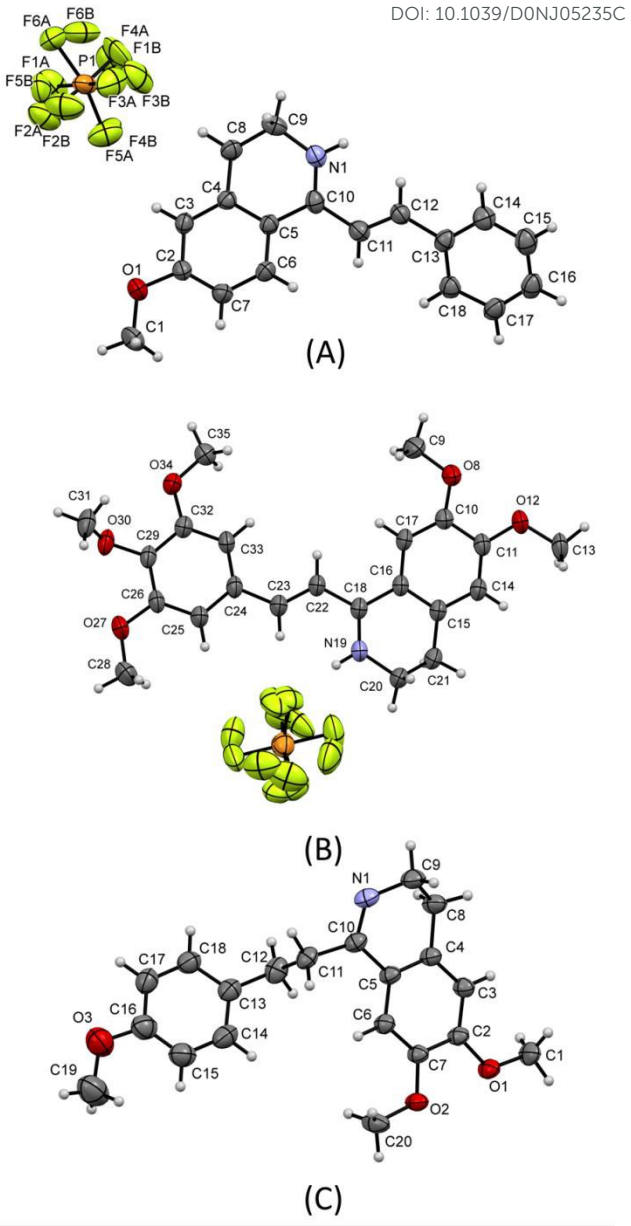

Fig. 2. Molecular structures of (A) **2a**, (B) **2b**, and (C) **2d**, showing displacement ellipsoids drawn at the 50% probability level. In case of **2b**, the crystal structure was reported in Puerto, *et al.* [15]

hexafluorophosphate **2b**, such channels are not present (Figure 5B), and the PF_6^- anions are occupying the 9.7% of the crystalline space with 112.6 Å^3 in the unit cell.

Considering the structural similarities and molecular dimensions, this behaviour constitutes an important feature considering that changes in the C10-N1-C9-C8 torsion angle (**2a**/**2d** numbering) could modify potential properties, such as 1-dimensional ion conductivity. The supramolecular assembly in compound **2a** is built mainly by the intermediation of the fluorophosphates groups which act as molecular linkers. These interactions were confirmed by the B3LYP-calculated Hirshfeld surface (Hs) mapped over d_{norm}. The H···F/F···H interactions constitute the 32.6 % of the total Hs showing a high

participation in the formation of the crystal (for details see ESI).

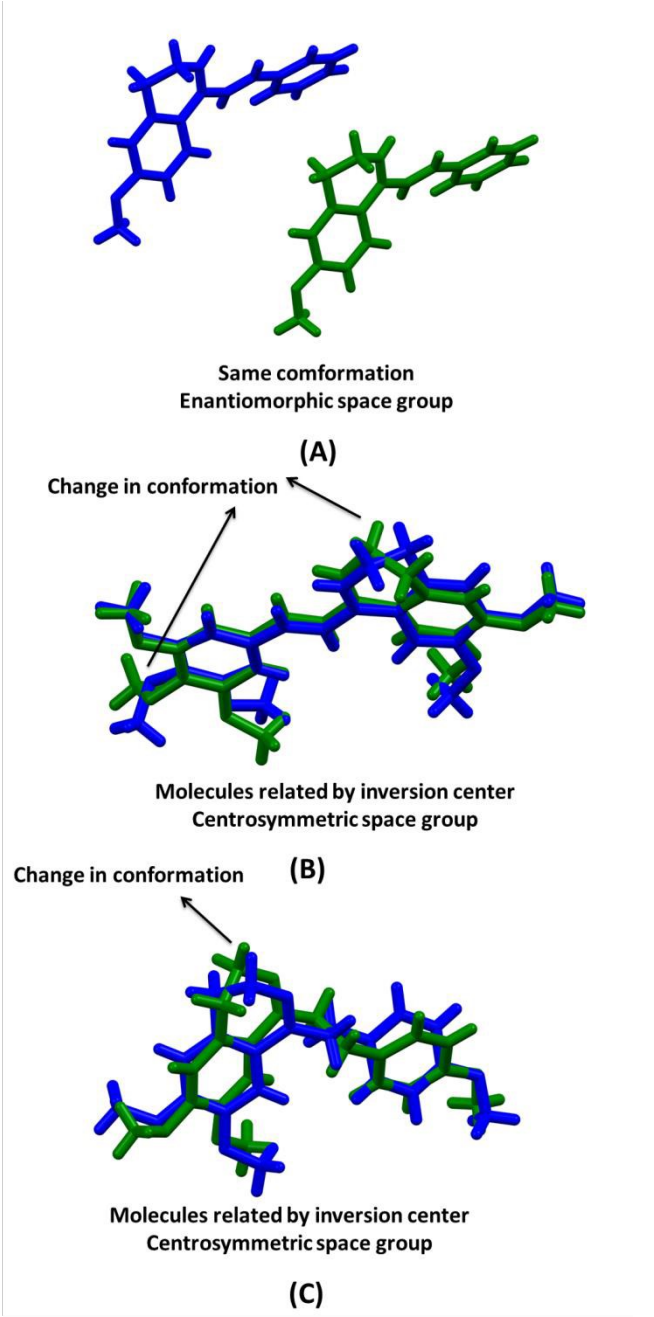

Fig. 3. (A) Compound **2a** crystallizing in an enantiomorphic $P6_1$ space group. (B) 3,4-dihydroisoquinoline-hexafluorophosphate **2b** crystallizing in a centrosymmetric *P*-1 space group. (C) Compound **2d** crystallizing in a centrosymmetric $P2_1/n$ space group.

As it was mentioned above, compound **2d** crystallizes in a centrosymmetric $P2_1/n$ space group. This means that both possible conformers are present. In fact, inversion-related molecules are connected by pairs of equivalent C9–H9A···O2^{iii} (symmetry code: (iii) -x,1-y,-z) hydrogen interactions to form dimers which are further connected by C1–H1A···O3^{iv} (symmetry code: (iv) 1-x,1-y,-z) contacts to grow chains along [100] direction (Figure 6A and Table 2). These connections constitute the 11.5% of the total Hirshfeld surface (for details see ESI). Between chains, C8–H8A···Cg1^{v} (symmetry code: (v) -1/2+x,1/2-y,-1/2+z; Cg1 is the centroid of the C13/C18 ring) interactions help to build the supramolecular assembly along [001] direction (Figure 6B and Table 2). This C8–H8A···π contact is interestingly strong (2.75 Å) compared with usual values (>2.8 Å). Along [-101] direction, π···π stacking interactions help to define the 3-dimensional structure (Figure 6B).

Table 2. Selected hydrogen-bond geometry (Å, °) for **2a** and **2d**.

2a				
D-H···A	**D-H**	**H···A**	**D···A**	**D-H···A**
N1–H1D···F5^{i}	0.86	2.14	2.98(2)	166
C12–H12···F3^{i}	0.93	2.48	3.375(19)	161
C1–H1B···F4^{ii}	0.96	2.18	3.10(2)	159
2d				
C9–H9A···O2^{iii}	0.97	2.63	3.465(4)	145
C1–H1A···O3^{iv}	0.96	2.72	3.505(5)	140
C8–H8A···Cg1^{v}	0.97	2.75	3.640	123

Symmetry codes: (i) y,1-x+y,-1/6+z; (ii) 1+x,1+y,z; (iii) -x,1-y,-z; (v) 1-x,1-y,-z. Cg1 is the centroid of the C13/C18 ring in **2d**

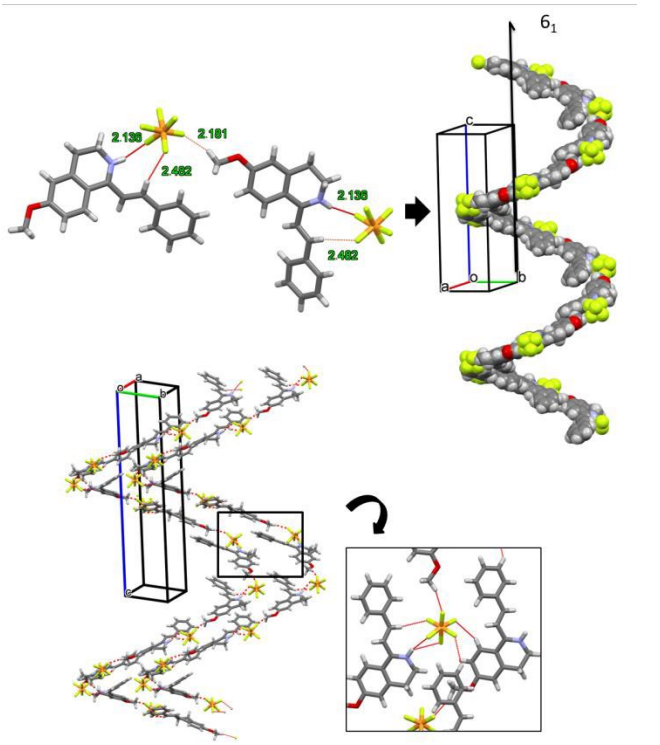

Fig. 4. (N,C)–H···F hydrogen interactions (2.14-2.50 Å) forming molecular spirals wrapped along *c* axis for compound **2a**. Between spirals, fluorophosphate ions act as molecular linkers through weaker (N,C)–H···F interactions (2.65 Å).

For this crystal (**2d**), some diffuse electronic densities were observed in the intermolecular voids which were related to disordered ethanol molecules. After several refinements involving disordered models, it was not possible to obtain a reasonable refined structure. Therefore, the SQUEEZE utility[29] in PLATON[29,30] was used to model its contribution to the

overall intensity data. In this case, the void spaces are present in localized positions with center at (1/2, 1/2, 1/2) of the unit cell, representing the 14.9 % of the structure and 314.6 Å^3 of the unit cell volume, as was observed for the 3,4-dihydroisoquinoline-hexafluorophosphate **2b** (Figure 6C). This behaviour confirms that the presence of both conformers induces a centrosymmetric structure. However, when only one conformer crystallizes, the solid grows in an enantiomorphic structure with the formation 1D-channels.

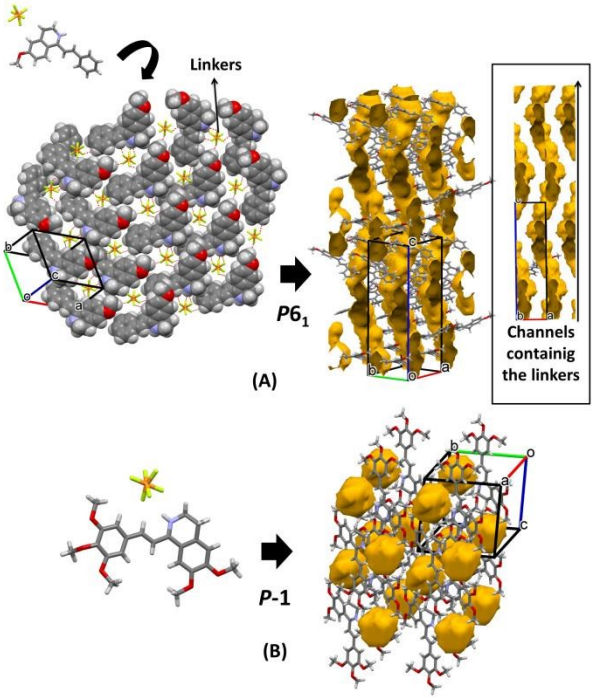

Fig. 5. (A) Fluorophosphate ions inside the channels directed along [001] in the enantiomorphic **2a** structure. (B) Fluorophosphate ions inside located voids in 3,4-dihydroisoquinoline-hexafluorophosphate **2b** crystallizing in a centrosymmetric *P*-1 space group.

CE-B3LYP model energies showed that a great contribution of electrostatic forces is involved in the formation of the molecular spirals in **2a**, connecting the fluorophosphate ions with the 6-methoxy-1-styryl-3,4-dihydroisoquinolin core (Figure 7A). However, as observed for the 3,4-dihydroisoquinoline-hexafluorophosphate **2b** these contacts are not enough to build a supramolecular assembly with defined 1D-channels that cross the structure. Apparently, the presence of one or two conformers induces a change in the symmetry of the crystal which determines the formation of the channels. In crystals **2a** and **2d**, dispersion forces have an important role in the formation of the solids (Figure 7), which was also observed in **2b**.[14] Pairwise interactions energies allowed the interpretation of the crystal packing in terms of energy, obtaining total packing energies of -173.6 and -135.0 kJ/mol for **2a** and **2d**, respectively, which was consistent with the presence of electrostatic forces of greater magnitude in **2a** (Figure 7).

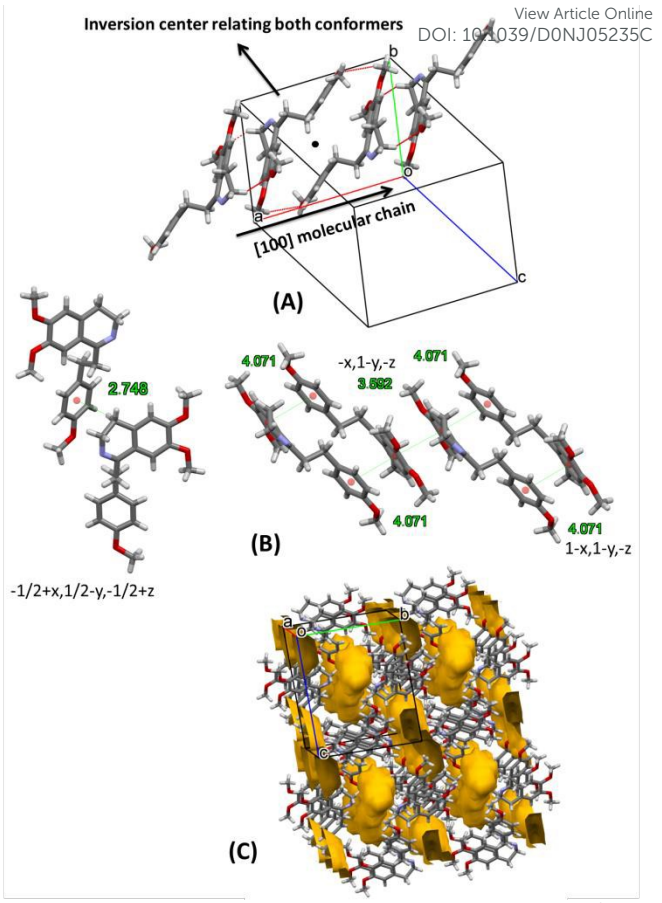

Fig. 6. The crystal structure of **2d**, showing (A) the C–H···O (Å), (B) C8–H8A···π and π···π interactions (Å). (C) Voids available for solvent molecules in **2d**.

4. Conclusions

In summary, we have demonstrated that controlling the reaction conditions of the Bischler-Napieralski reaction 3,4-dihydroisoquinolines from *N*-phenylethyl cinnamamides can be obtained as a free base or as hexafluorophosphate salts in good to excellent yields. In this study, a 1-phenethyl-3,4-dihydroisoquinoline derivative was crystalized and fully characterized for the first time by X-ray crystallographic techniques, being an important intermediate in the total synthesis of natural isoquinoline metabolites. In general, X-ray analysis of 3,4-dihydroisoquinolines showed that the torsion angle C10-N1-C9-C8 (**2a**/**2d** numbering) in the dihydroisoquinoline fragment allows the formation of two inversion-related conformers. The presence of both conformers induces a centrosymmetric crystal structure. However, when only one conformer crystallizes, an enantiomorphic crystal structure, with $P6_1$ space group in the case of **2a**, is formed. The 6-fold screw axis parallel to [001] direction describes a spiral-like molecular behaviour with 1-D channels containing the fluorophosphate ions. This feature allows us to imagine a potential structural modulation based on the crystallization of one or both possible conformers.

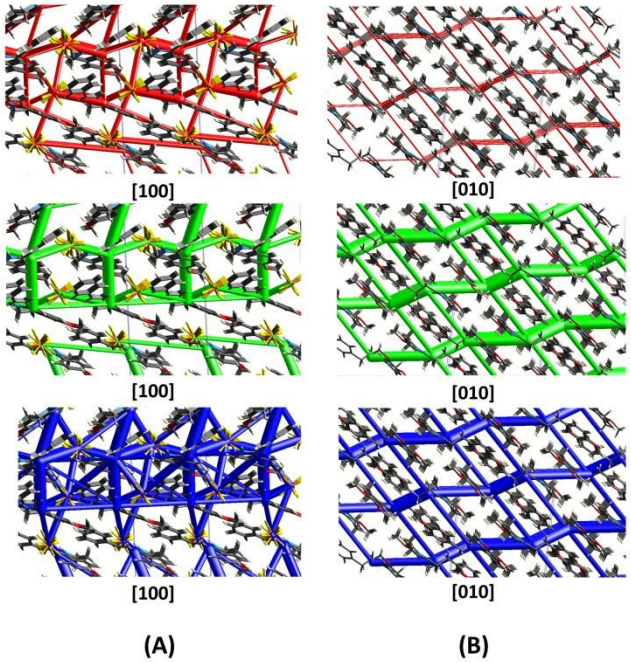

Fig. 7. Energy framework diagrams for electrostatic (red) and dispersion (green) contributions to the total interaction energies (blue) in (A) **2a** viewed along [100], and (B) **2d** viewed along [010].

Conflicts of interest

There are no conflicts to declare.

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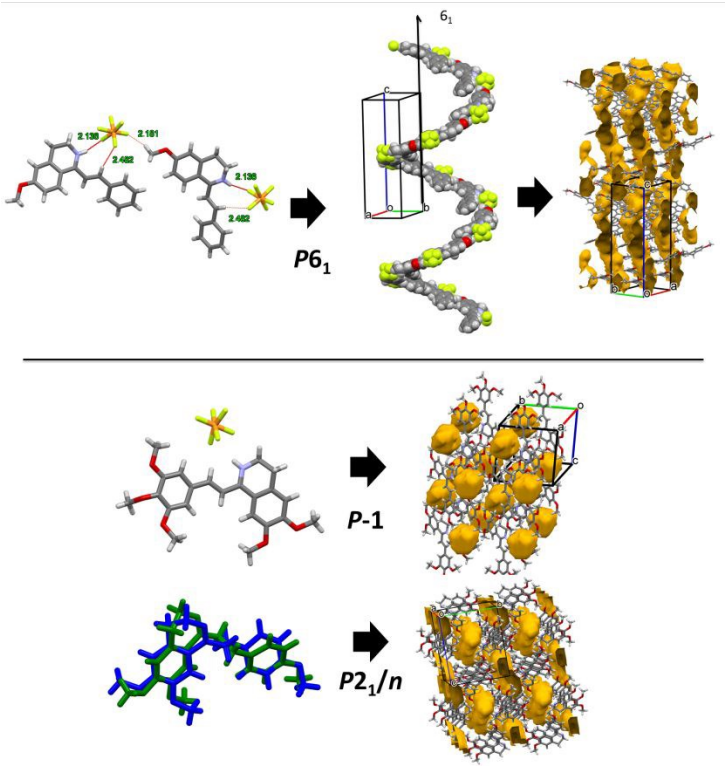

Free base and hexafluorophosphate salts of 3,4-dihydroisoquinolines from the Bischler-Napieralski reaction: potential supramolecular modulation. Centrosymmetric/enantiomorphic crystals