Microwave-assisted synthesis of a new fluorinated Biphenyl-Schiff base with potential application in nonlinear optical

Síntese assistida por micro-ondas de uma nova Bifenil-Base de Schiff Fluorada com potencial aplicação em óptica não linear

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ABSTRACT
The new fluorinated Biphenyl-Schiff Base 3 was synthesized by a synthetic route involving three steps, with the formation of two intermediates precursors. Primarily by the result of a Suzuki-Miyaura cross-coupling reaction forming the fluorinated 4-aminobiphenyl (1) and later by the result of the nucleophilic substitution SN2 obtaining the intermediate 4-[2-(dimethylamino)ethoxy]-benzaldehyde (2). The Schiff base 3 was obtained through the condensation reaction between intermediates 1 and 2. The methodology involving the reaction to form intermediate 2 proved to be more effective when aided by microwave irradiation providing a significantly higher yield in a shorter time. The GC-MS showed that all compounds were synthesized by the proximity of the calculated m/z ratio and that found. In addition, theoretical calculations showed that the
new fluorinated Biphenyl-Schiff Base 3 obtained a value for the first hyperpolarizability ($\beta_t$) of $45.1 \times 10^{-30}$ esu that is approximately five times greater than the experimental value of $9.2 \times 10^{-30}$ esu for the reference compound (p-nitroaniline).

**Keywords:** Schiff Base, Biphenyl, Nonlinear Optical Properties, First Hyperpolarizability, Suzuki-Miyaura, Microwave.

**RESUMO**

A inédita Biphenil-Base de Schiff fluorada 3 foi sintetizada através de uma rota sintética envolvendo três etapas, tendo a formação de dois intermediários precursos, primeiramente pelo resultado de uma reação de acoplamento cruzado Suzuki-Miyaura formando a 4-aminobifenila fluorada (1) e, posteriormente, pelo resultado da substituição nucleofílica S_N2 obtendo o intermediário 4-(2-(dimetilamino)etoxi)-benzaldeído (2). A base de Schiff 3 foi sintetizada através da reação de condensação entre os intermediários 1 e 2. A metodologia envolvendo a reação para formação do intermediário 2 mostrou ter maior eficácia quando assistida por micro-ondas fornecendo um rendimento significativamente mais alto em um menor tempo reacional. O CG-EM mostrou que todos os compostos foram sintetizados pela proximidade da relação m/z calculada e a encontrada. Somado a isso, cálculos teóricos mostraram que a base de Schiff-fluorada 3 obteve um valor para a primeira hiperpolarizabilidade ($\beta_t$) de $45.1 \times 10^{-30}$ esu, que é aproximadamente cinco vezes maior que o valor experimental de $9.2 \times 10^{-30}$ esu do composto de referência (p-nitroanilina).

**Palavras-chave:** Base de Schiff, Biphenil, Óptica Não Linear, Primeira Hiperpolarizabilidade, Suzuki-Miyaura, Micro-ondas.

**1 INTRODUCTION**

Nonlinear optics (NLO) studies the interactions of matter with light, and materials with this type of property can be used for the development of new optical systems, with applications in data storage, sensors, signal processing, and others (BALDWIN, 1917; FRANKEN et al., 1961; GARMIRE, 2013, KANIS et al., 1994)). In this sense, organic compounds with nonlinear optical properties (NLO) have been the subject of intensive studies in recent decades (CHENG et al, 1991a; CHENG et al., 1991b; GHANAVATKAR et al., 2021; PAPAGNI et al., 2002). Organic materials offer greater flexibility and can offer a lower production cost when compared to inorganic materials (KHALID et al., 2020). Besides, nonlinearity is related to molecular polarizability, that is, the degree of charge separation. This phenomenon can be intensified by a $\pi$-type conjugate system, making the electron distribution highly deformable in the presence of electric fields, which facilitates the induction of polarizations [5,6]. An example of such systems are the organic push-pull molecules, which include a donor and acceptor group
connected by a $\pi$ conjugation. (CASTET et al., 2021; PAPAGNI et al., 2002; UNDAVALLI et al., 2021).

Therefore, the addition of phenyl groups as the biphenyl or heteroaromatic biaryl portions in the structure of organic molecules favors the NLO properties. These molecules when substituted by donor and acceptor groups, form asymmetric compounds with a high value for the first hyperpolarizability (AMATORE et al., 1990; LEDOUX et al., 1991; ZHANG et al., 2021). In addition to the increase in the combined system, the types of donor and acceptor groups that can intensify ownership are also sources of study. The fluorine atom is a potential candidate for the acceptor group due to its high electronegativity and size, making the molecule polarized without altering the planarity, avoiding possible steric effects [12–15].

Since the experimental determination of the first hyperpolarizability is a difficult task, the quantum mechanics calculations are an excellent alternative to solve this problem (MILLER et al., 1988; PASCHOAL et al., 2010; SEKINO et al., 1993). However, the theoretical description of the NLO properties presents a significant dependence on factors such as basis sets and electronic correlation (MAROULIS, 1996, 1998, 2003, 2012). In previous papers (PASCHOAL et al., 2013, 2016), we studied the NLO properties of a wide range of organic molecules with push-pull groups using the NLO-V basis sets, which was developed specifically for the study of NLO properties, with the CAM-B3LYP DFT functional, which the calculated results for the first hyperpolarizability obtained an excellent agreement with the experimental values.

Thus, in the present paper, we synthesize a new push-pull type fluorinated Biphenyl-Schiff Base and we carry out theoretical studies of its nonlinear optical properties to evaluate a potential application in optical devices.

2 EXPERIMENTAL SECTION

2.1 MATERIALS

The reagents p-iodoaniline, p-hydroxyaldehyde, 2,4-difluorophenylboronic acid, palladium acetate, sodium carbonate, potassium carbonate and 2-Chlorine-N,N-dimethylethanamine hydrochloride were purchased by Sigma-Aldrich® and PEG1500 by Dinâmica®. All solvents were purchased by Tedia (USA)® without previous purification. The syntheses were performed on the Anton Paar Monowave 300 equipment and mass spectrometry analyzes coupled with gas chromatography (GC-MS) were
performed at the analytical center of the Farmanguinhos-FIOCRUZ (RJ) on a WATERS/MICROMASS equipment.

2.2 SYNTHESIS OF 2',4'-DIFLUORO-[1,1'-BIPHENYL]-4-AMINE – 1

In a 30 mL vial, 2,4-difluorophenylboronic acid (1.5 mmol), p-iodoaniline (1 mmol), palladium acetate (0.01 mmol) and sodium carbonate (2 mmol) were added, along with a mixture of H₂O: PEG1500 (3 g: 3.5 g). The reaction was carried out by 60 min at 100 °C. After the end of the reaction accompanied by thin-layer chromatography (TLC), the solution was extracted with diethyl ether (4 x), the organic phases were combined and dried over anhydrous sodium sulfate and active carbon. The organic phase was filtered off over celite® and the solvent was removed. The product was purified by recrystallization from ethanol to form a white solid, \( \eta = 50\% \). The GC-MS chromatogram found m/z= 205 for \( \text{C}_{12}\text{H}_{9}\text{F}_{2}\text{N} \).

2.3 SYNTHESIS OF 4-[2-(DIMETHYLAMINO)ETHOXY]-BENZALDEHYDE – 2

The preparation of intermediate 2 was carried out by changing the parameters: temperature, time, and solvent (Table 1). Initially, p-hydroxyaldehyde (1 mmol) was added together with potassium carbonate (3 mmol). In the second step, 2-Chloro-\( N,N \)-dimethylethanamine hydrochloride (1 mmol) was added to the reaction medium. The product was purified through a flash chromatographic column on silica gel, using ethanol as eluent, resulting in a yellow oil. The GC-MS chromatogram found m/z= 193 for \( \text{C}_{11}\text{H}_{15}\text{NO}_{2} \).

2.4 SYNTHESIS OF FLUORINATED BIPHENYL-SCHIFF BASE 3

The compounds 1 (0.5 mmol) and 2 (0.5 mmol) with a catalytic amount of acetic acid (1 drop) were dissolved in 15 mL of ethanol in a 30 mL vial. The system was kept under microwave irradiation for 45 min at 145 °C, resulting in a yellow solid, purified by recrystallization in ethanol, \( \eta = 26\% \). The GC-MS chromatogram found m/z= 380 for \( \text{C}_{23}\text{H}_{22}\text{F}_{2}\text{N}_{2}\text{O} \).

2.5 THEORETICAL METHODOLOGY

The structure of the new fluorinated biphenyl-Schiff base 3 was constructed using the Avogadro 1.2 program (AVOGADRO; HANWELL, 2012) and its structure was optimized and characterized as a minimum point on the potential energy surface (PES).
through harmonic frequency calculations at the B3LYP/6-31G(d) level. Subsequently, finite field (FF) (KURTZ, 1990) calculation at CAM-B3LYP/NLO-V was performed to extract the tensor elements of the first hyperpolarizability ($\beta_{ijk}$) and the total first hyperpolarizability of the molecule was calculated as eqs. (01) and (02). Solvent effects were considered in both structure and NLO calculations using the Conductor-like Continuum Polarization Model (C-PCM) with the dielectric constant set for ethanol. The NLO-V basis sets can be downloaded free of charge from the Supplementary Material of Paschoal and Dos Santos (2012) and the Basis Set Exchange Portal (PRICHARD, 2019) (https://www.basissetexchange.org/).

$$\beta_t = \sqrt{\beta_x^2 + \beta_y^2 + \beta_z^2}$$  \hspace{1cm} (01)

where

$$\beta_i = \beta_{iii} + \frac{1}{3} \sum_{ij} (\beta_{ij} + \beta_{ji} - \beta_{jj})$$  \hspace{1cm} (02)

All calculations were carried out using the GAMESS 2020 R2 program (BARCA, 2020).

3 RESULTS AND DISCUSSION

3.1 SYNTHESIS AND CHARACTERIZATION BY GC-MS

The new fluorinated biphenyl-Schiff base 3 was designed from the condensation between intermediates 1 and 2, as shown in the retrosynthesis in Figure 1. All compounds were characterized by the Gas Chromatography coupled to Mass Spectrometry technique (GC-MS). According to the mass spectrum of the compounds, it is evident that the derivatives were synthesized as expected.
The intermediate 1 was synthesized from the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction, in an aqueous system (H\textsubscript{2}O: PEG1500) under microwave irradiation [16,17], 99.3% conversion of the expected product was observed by the GC-MS. After purification, by recrystallization, fluorinated intermediate 4-aminobiphenyl 1 was obtained in 50% yield. The synthetic methodology for the formation of intermediate 2 was studied, as detailed in Table 1 [18,19]. According to the results obtained, it was possible to observe that the reaction from entry 2 furnished a higher yield when compared to the others. This data shows the influence of the solvent (acetone and PEG400) and the temperature (RT and 60° C). PEG400 is a polymer that appears as a colorless liquid at room temperature (different from the PEG1500 used in the Suzuki-Miyaura reaction - previous step - which is a white solid) and is widely used in organic synthesis due to its high polarity [20–22]. In this case, the reaction is a bimolecular nucleophilic substitution (S\textsubscript{N}2), therefore aprotic polar solvents, such as acetone, make the nucleophile stronger (competitive) due to the decrease in the solvation effect. On the other hand, the increase in temperature is directly linked to the reaction kinetics, which in turn increases the number of collisions between the nucleophile and the electrophile, with a greater possibility of effective attack. [23].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time Step 1</th>
<th>Time Step 2</th>
<th>Aldehyde</th>
<th>Chloridrate</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEG400</td>
<td>30 min</td>
<td>5h</td>
<td>2 equiv.</td>
<td>1 equiv.</td>
<td>RT</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Acetone</td>
<td>2h</td>
<td>2h</td>
<td>1 equiv.</td>
<td>1.4 equiv.</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>PEG400</td>
<td>2h</td>
<td>2h</td>
<td>1 equiv.</td>
<td>1.4 equiv.</td>
<td>RT</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>PEG400</td>
<td>2h</td>
<td>2h</td>
<td>1 equiv.</td>
<td>1.4 equiv.</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>PEG400</td>
<td>30 min</td>
<td>24h</td>
<td>2 equiv.</td>
<td>1 equiv.</td>
<td>RT</td>
<td>16</td>
</tr>
</tbody>
</table>

RT = room temperature
Since the methodology used in entry 2 (Table 1) was the best, this reaction was reproduced with microwaves irradiation. The result showed that even with a significant decrease in reaction time, the product was obtained with 65% yield (Table 2). The yield increase is directly linked to homogeneous heating via microwave irradiation, due to the oscillation between the applied electric field and the dipoles present in the reaction medium, which lose energy in the form of heat due to molecular shocks [24,25].

Table 2. Results of the S_N2 reaction methodology in acetone varying the reaction time of the microwave-assisted reaction and conventional heating.

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>CH</td>
<td>240</td>
<td>29</td>
</tr>
</tbody>
</table>

*MI = Microwave irradiation; CH = Conventional Heat

The microwave-assisted synthesis to obtain the new fluorinated Biphenyl-Schiff base 3 was carried out by a simple condensation between intermediates 1 and 2 in ethanol as solvent. That is a classic reaction of nucleophilic addition between aldehyde and primary amine to form imine (Schiff base) in an acidic medium. Purification by recrystallization from ethanol furnished a yellow solid in 26% yield.

The products synthesized in this work were confirmed by were accompanied by thin-layer chromatography (TLC) and characterized by GC-MS. The mass spectrometry chromatograms (Fig. 2) show the difference between the products obtained 1, 2 and 3 by the ion-molecular peak of each compound. For intermediate fluorinated 4-aminobiphenyl 1 the m/z= 205 was found for C_{12}H_{9}F_{2}N (A), intermediate 2, m/z= 193 was found for C_{11}H_{15}NO_{2} (B). The chromatogram of the new Biphenyl-Schiff base 3 proposed in this work found the ion-molecular peak m/z= 380 for C_{23}H_{22}F_{2}N_{2}O (C).
3.2 NONLINEAR OPTICAL STUDY

The phenomenon of nonlinear optics has a wide range of applications in areas such as information technology, lasers, and in the interaction with materials (GARMIRE, 2013). At the molecular level, the main NLO response of interest is the first hyperpolarizability ($\beta$) (GHANAVATKAR, 2021). Thus, the total first hyperpolarizability ($\beta_t$) of the new fluorinated biphenyl-Schiff Base 3 (Fig. 3a) was calculated at CAM-B3LYP/NLO-V/C-PCM//B3LYP/6-31G(d)/C-PCM level as eqs. (01) and (02) and compared with the experimental value of the reference p-nitroaniline (PNA) molecule (Fig. 3b).
Figure 3. (a) Optimized geometry at B3LYP/6-31G(d)/C-PCM level and calculated first hyperpolarizability at CAM-B3LYP/NLO-V/C-PCM level for the title compound 3. (b) Reference p-nitroaniline (PNA) molecule with its experimental value for the first hyperpolarizability. The structures were obtained with the Chemcraft program (CHEMCRAFT).

The \( \beta_t \) calculated value was \( 45.1 \times 10^{-30} \) cm\(^5\) esu\(^{-1}\), which is 4.90 times more than the magnitude of reference PNA \( (9.2 \times 10^{-30} \) cm\(^5\) esu\(^{-1}\)). Molecules with a high value of the first hyperpolarizability are important for the development of organic materials with second-order nonlinear optical responses. The pronounced increase in the \( \beta_t \) value for the title compound 3 compared to the reference compound (PNA) can be explained by the structure of the molecule, which in turn, has a larger conjugated system than the reference, increasing the push-pull effect and consequently the separation of charges. Another point is the insertion of fluorine atoms, with high polarization of the C-F bond due to the presence of the low energy of \( \sigma^* \) antiligant orbital [2,5,13,26].

4 CONCLUSIONS

The compounds proposed in the present paper were synthesized as expected and characterized by GC-MS. The Suzuki-Miyaura cross-coupling reaction via microwave irradiation provided the intermediate fluorinated 4-aminobiphenyl 1 with a 50% yield. It
was observed that microwave irradiation was shown to be more effective in the $S_{N2}$ reaction to form intermediate 2, reducing the reaction time to 30 min, in addition to increasing the expected product yield (65%). The synthesis of the new fluorinated biphenyl-Schiff base 3 was also carried out under microwave irradiation through the condensation of intermediates 1 and 2 in an acid medium with 26% yield. Theoretical calculations for the first hyperpolarizability ($\beta_1$) showed that the title Schiff base 3 has a high potential for the formation of optical devices, having a value approximately five times higher than the reference $p$-nitroaniline molecule. This result highlights the importance of the increase in phenyl groups, provided by biphenyl and the high separation of charges from the group N,N-dimethylamine (N(CH$_3$)$_2$) and fluorine atoms.
REFERENCES


