Selective Arylation of 2-Bromo-4-chlorophenyl-2-bromobutanoate via a Pd-Catalyzed Suzuki Cross-Coupling Reaction and Its Electronic and Non-Linear Optical (NLO) Properties via DFT Studies

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Abstract: In the present study, 2-bromo-4-chlorophenyl-2-bromobutanoate (3) was synthesized via the reaction of 2-bromo-4-chlorophenol with 2-bromobutanoil bromide in the presence of pyridine. A variety of 2-bromo-4-chlorophenyl-2-bromobutanoate derivatives (5a–f) were synthesized with moderate to good yields via a Pd-catalyzed Suzuki cross-coupling reaction. To find out the reactivity and electronic properties of the compounds, Frontier molecular orbital analysis, non-linear optical properties, and molecular electrostatic potential studies were performed.

Keywords: suzuki cross coupling; frontier molecular orbital analysis; molecular electrostatic potential; non-linear optical properties

1. Introduction

Carboxylic esters are an important class of organic compounds, having various biological activities such as antifungal [1], antioxidant [2], anti-inflammatory [3], antiproliferative [4], and anti-bacterial [5], and they have been widely used in the biofuel [6], plasticizer [7], food, and cosmetic industries [8].
In natural product chemistry, esters are well known common intermediates because of their accessibility for easy interconversion and their stability. Esters are generally synthesized by the condensation of carboxylic acids with alcohols. Moreover, activation of the carboxyl group followed by reaction with suitable alcohol is one of the most familiar methods for ester formation [9]. Similarly, biphenyl compounds are used as central building blocks for basic liquid crystal [10] and fluorescent layers in organic light-emitting diodes (OLEDs) [11] and are also important pharmaceutically as anti-hypertensive [12], anti-inflammatory [13], potential anti-cholinesterase [14], anti-diabetic [15], anti-tumor [16], anti-cancer [17], and anti-leukemia agents [18], and as potential therapeutics for cardiovascular disease [19] and osteoporosis [20].

For the synthesis of biphenyl compounds, the Suzuki–Miyaura reaction is one of the best methods. In organic synthesis, regioselective functionalization plays a progressively important role [21]. In such types of reactions, the reaction takes place at the carbon atom, which is more electron-deficient, while the other active site remains unattached. This concept has been practiced in region-selective Pd-catalyzed cross-coupling reactions based on different rates of oxidative additions of Pd (0) species to carbon halide bonds of different substrates. Therefore, we focused on the synthesis of 2-bromo-4-chlorophenyl-2-bromobutanoate followed by regioselective arylation of 2-bromo-4-chlorophenyl-2-bromobutanoate via a palladium-catalyzed Suzuki–Miyaura cross-coupling reaction to obtain the 2-bromo-4-chlorophenyl-2-bromobutanoate derivatives. Frontier molecular orbital (FMO), non-linear optic properties (NLO) and molecular electrostatic potential (MEP) studies were performed to find out the most reactive site of the compound.

2. Results and Discussion

2.1. Chemistry

In the present study, 2-bromo-4-chlorophenyl-2-bromobutyrate (3) was synthesized by the reaction of 2-bromo-4-chlorophenol (1) with 2-bromobutyl bromide (2) in the presence of pyridine and acetonitrile, and good yield of 2-bromo-4-chlorophenyl-2-bromobutanoate (3) was observed (Scheme 1).

![Scheme 1](image)

Scheme 1. Synthesis of 2-bromo-4-chlorophenyl-2-bromobutyrate (3). Conditions: (i) 1 (1 g, 4.820 mmol), 2 (0.64 mL, 5.3 mmol), pyridine (0.7 mL, 9.63 mmol), MeCN (30 mL), 0 °C, 1 h.

In addition, the Suzuki–Miyaura cross-coupling reaction of 2-bromo-4-chlorophenyl-2-bromobutyrate (3) with different phenyl boronic acids was accomplished, which ultimately led to the formation of the corresponding 2-bromo-4-chlorophenyl-2-bromobutyrates (5a–f) in moderate to good yields (64–81%) (Scheme 2, Table 1). When 1.1 eq of phenyl boronic acid was used, it was noted that the bromo group of the phenyl group was replaced, while in the presence of Pd (PPh3)4, the other bromo group present at the alpha position could not be replaced. The chloro group at the phenyl ring was not replaced due to the C-Cl bond strength that obstructs the reactivity of aryl chlorides, thus, they are resistant to the oxidative addition to Pd(0) because activation of aryl chlorides is much more difficult than that of aryl bromides. The oxidative addition step is a selectivity-determining step in Suzuki cross-coupling, and it is broadly controlled by the bond dissociation energies of the carbon–halogen bond that predictably differs as a function of the aryl halides: Ar-I > Ar-Br > Ar-Cl > Ar-F [22]. It was
noted that phenyl boronic acids having electron-donating substituents gave high yields as compared to electron-withdrawing substituted phenyl boronic acids.

Scheme 2. Synthesis of 2-aryl-4-chlorophenyl-2-bromobutyrates (5a–f). Conditions: (i) 3 (200 mg, 0.062 mmol, 1 eq), 4 (0.683 mmol, 1.1 eq), Pd (PPh$_3$)$_4$ (35 mg, 5 mol %), K$_3$PO$_4$ (263 mg, 1.24 mmol, 2.2 eq), 1, 4-dioxane (8 mL), water (4 mL), 90 °C, 17 h under argon.

Table 1. Suzuki–Miyaura reaction of 2-bromo-4-chlorophenyl-2-bromobutyrate with different phenyl boronic acids.

| Sr. No. | Phenyl Boronic Acid | Products | Solvent/H$_2$O (4:1) | Yield % |
|---------|---------------------|----------|----------------------|---------|
| 5a      | 3-Cl-4-F-C$_6$H$_4$  |          | 1,4-dioxane          | 64      |
| 5b      | 3-(MeCO$_2$)-C$_6$H$_4$ |        | 1,4-dioxane          | 76      |
| 5c      | 4-(MeS)-C$_6$H$_4$   |          | 1,4-dioxane          | 79      |
| 5d      | 3,4-Cl$_2$-C$_6$H$_4$|          | 1,4-dioxane          | 68      |
The energies of HOMOs (E_{HOMOs}) and LUMOs (E_{LUMOs}) provide information about the electronic transition and the HOMOs–LUMOs gap (G_{H-L}) explains the reactivity and kinetic stability of the compounds. If the G_{H-L} is low, the compound will be less stable and more reactive, but if the G_{H-L} is large, the compound will be highly stable and less reactive [24]. The energies of HOMOs (E_{HOMOs}), energies of LOMOs (E_{LUMOs}), and the highest occupied molecular orbital to lowest unoccupied molecular orbital gap (G_{H-L}) are summarized in Table 2.

Table 2. The energies of HOMOs (E_{HOMOs}, in eV), energies of LUMOs (E_{LUMOs}, in eV) HOMOs–LUMOs gap (G_{H-L}), and dipole moment (\(\mu\), in Debye) of compounds (5a–f).

| Compounds | E_{HOMOs} | E_{LUMOs} | G_{H-L} |
|-----------|-----------|-----------|---------|
| 5a        | -7.06     | -1.93     | 5.14    |
| 5b        | -7.03     | -1.97     | 5.06    |
| 5c        | -6.06     | -1.79     | 4.27    |
| 5d        | -7.07     | -1.98     | 5.09    |
| 5e        | -6.30     | -1.73     | 4.57    |
| 5f        | -7.06     | -1.87     | 5.19    |

Among all compounds, compound 5c has the lowest G_{H-L} (4.27 eV) where the E_{HOMOs} and E_{LUMOs} were -6.06 and -1.79 eV, respectively. Based on the lower G_{H-L}, 5c is considered as kinetically less stable and moderately reactive. Compound 5f has G_{H-L} of 5.19 eV, which showed it is the most stable and least reactive of the whole series (5a–f). The G_{H-L} of the other compounds were between 4.57 and 5.14 eV, which represent their moderate reactivity and sufficient stability. Although the G_{H-L} of 5c is low, compared to other compounds, it is large.

The iso-density distributions in the FMOs of all compounds were also shown in Figure 1. In all the compounds (except compounds 5c and 5e), the iso-density of HOMOs was distributed on the phenyl rings and halogen (chlorine and fluorine) groups that were present on the phenyl rings. However, this iso-density of HOMOs is shifted from the chlorine-containing phenyl ring towards the MeS- and MeO-groups containing phenyl rings in compounds 5c and 5e, respectively. This specific distribution explains the lower iso-density of 5c and 5e compared to that of the other compounds. The shift of iso-density is more pronounced for 5c in comparison to 5e. The iso-density of LUMOs is mostly distributed on the bromo-ester group attached to the phenyl ring in all compounds (5a–f).
2.3. Reactivity Descriptor Parameters

For further elucidation of the reactivity of these compounds (5a–f), some other reactivity descriptor parameters were also studied. The results of the analyses are given in Table 3. These parameters include ionization potential ($I$), electrophilicity index ($\Theta$), nucleophilicity (N), electron affinity ($EA$), electronic chemical potential ($\mu$), and chemical hardness ($\eta$). According to Koopman’s theorem, the negative of HOMOs and LUMOs values correspond to the ionization potential ($I$) and electron affinity ($EA$), respectively [25].

Table 3. Ionization potential ($I$), electron affinity ($EA$), chemical hardness ($\eta$), electronic chemical potential ($\mu$), electrophilicity index ($\Theta$), and nucleophilicity (N) of compounds (5a–f). All values are given in eV.

| Compounds | Ionization Potential ($I$) | Electron Affinity ($EA$) | Chemical Hardness ($\eta$) | Electronic Chemical Potential ($\mu$) | Electrophilicity Index ($\Theta$) | Nucleophilicity (N) |
|-----------|---------------------------|--------------------------|---------------------------|--------------------------------------|----------------------------------|----------------------|
| 5a        | 7.06                      | 1.93                     | 2.57                      | -4.50                                | 3.94                             | 5.14                 |
| 5b        | 7.03                      | 1.97                     | 2.53                      | -4.50                                | 4.00                             | 5.06                 |
| 5c        | 6.06                      | 1.79                     | 2.13                      | -3.92                                | 3.61                             | 4.27                 |
| 5d        | 7.07                      | 1.98                     | 2.55                      | -4.52                                | 4.02                             | 5.09                 |
| 5e        | 6.30                      | 1.73                     | 2.29                      | -4.01                                | 3.52                             | 4.57                 |
| 5f        | 7.06                      | 1.87                     | 2.60                      | -4.46                                | 3.83                             | 5.19                 |

2.3.1. Ionization Potential, Electron Affinity, and Chemical Hardness ($\eta$)

The Chemical hardness is mathematically expressed as:

$$\text{Chemical hardness ($\eta$)} = (E_{\text{HOMO}} - E_{\text{LUMO}})/2$$ (1)
The values obtained for all compounds from different reactivity descriptor are comparable and support each other, which strengthens our findings. The ionization potential of all compounds was in the range of 6.06 eV to 7.06 eV. The most reactive and unstable compound in this series was 5c, and its reactivity was also supported from its lower ionization potential ($I = 6.06$ eV), electron affinity ($E_A = 1.79$ eV), and chemical hardness ($\Pi = 2.13$ eV) values. The compound 5f was the most stable compound, which is also confirmed from its high $I$ (7.06 eV) and $\Pi$ (2.60 eV) values. The chemical hardness of the other compounds was between 2.13 and 2.57 eV.

2.3.1. Electronic Chemical Potential (µ)

The electronic chemical potential gives us an idea about the charge transfer inside compounds at their ground state, and it is mathematically expressed as:

$$\text{Electronic chemical potential (µ)} = \frac{(E_{\text{HOMO}} + E_{\text{LUMO}})}{2}$$

The electronic chemical potential (µ) of all compounds (5a–f) was in the range of $-3.92$ eV to $-4.52$ eV. The highest µ ($-4.52$ eV) value was observed for 5d and the lowest µ value ($-3.92$ eV) was calculated for 5c.

2.3.3. Electrophilicity Index (σ)

Parr et al. provided the concept of the electrophilicity index (σ) [26], which is mathematically expressed as:

$$\text{Electrophilicity index (σ)} = \frac{\mu^2}{\Pi}$$

According to this concept, the σ is the stabilization of a compound based on energy when an additional charge is transferred from the surroundings or outside environment. The σ ranged from 3.52 eV to 4.02 eV for compounds 5a–f. The compound 5e had the lowest σ value (3.52 eV) in the series of compounds, which indicates that this compound is less stable for an incoming charge. The reason is the electronic acceptor and donor groups present in the compound are connected through extended conjugation. The incoming charge causes further delocalization of electronic density in the compound and enhances its reactivity.

2.3.2. Nucleophilicity (N)

Nucleophilicity is derived from HOMOs and LUMOs values by using the following mathematical equation:

$$\text{Nucleophilicity (N)} = E_{\text{HOMO}} - E_{\text{LUMO}}$$

Nucleophilicity is an important parameter for understanding the reactivity of compounds. All the compounds had nucleophilicity values in the range of 4.27 eV to 5.19 eV. The compound 5c had the lowest N value (4.27 eV), which represents the soft nucleophilic nature of this compound. Whereas compound 3’5-Dichloro-[1,1’-biphenyl]-2-yl 2-bromobutanoate (5f) has the highest N value (5.19 eV), which shows the strong nucleophilic nature of this compound.

2.4. Molecular Electrostatic Potential (MEP)

Molecular electrostatic potential (MEP) is used to evaluate and predict the reactive sites of a molecule [27]. MEP is generated on the surfaces of all optimized compounds to explain the nucleophilic and electrophilic sites. The potentials on the surfaces of complexes are characterized by various colors and are described in increasing order of red < orange < yellow < green < blue. The green colors show the neutral region while red and blue colors are used for the nucleophilic and electrophilic sites of the complex, respectively. The molecular electrostatic surfaces of all compounds are given in Figure 2 and the values are given in Table 4.
For the last decade, scientific society has been pursuing the pathways to synthesized non-linear optical (NLO) materials with large second-order nonlinear optical properties. Non-linear optical materials have various applications in laser devices, optical communication, optical data storage, optical limiting, optical computing, and medical imaging [28, 29]. The NLO response of these materials is measured by the first hyperpolarizability ($\beta$). In organic molecules, the movement of electrons from donor to acceptor group is responsible for the enhancement of $\beta$, which ultimately results in a strong NLO response.

2.5. Non-linear Optical (NLO) Properties

Figure 2 indicates that the ester group attached to the phenyl ring is an active site for an incoming electrophile. Whereas, hydrogen attached to the phenyl rings have blue electronic densities that represent the strong nucleophilic site. Yellow densities reside on the S atom of the MeS, O of the MeO, Cl, and F atoms, illustrating the moderately electrophilic sites of these functional groups. The highest electronic density distribution of $-4.75 \times 10^{-2}$ to $4.75 \times 10^{-2}$ was observed for compound 5d. In contrast, the lowest electronic density distribution of $-5.22 \times 10^{-2}$ to $5.22 \times 10^{-2}$ was observed for compound 5e.

The NLO response of these materials is measured by the first hyperpolarizability ($\beta$). In organic molecules, the movement of electrons from donor to acceptor group is responsible for the enhancement of $\beta$, which ultimately results in a strong NLO response.

Table 4. Molecular electrostatic potential (MEP) values of all compounds (5a–f).

| Compounds | –ve Potential | +ve Potential |
|-----------|--------------|--------------|
| 5a        | $-4.77 \times 10^{-2}$ | $4.77 \times 10^{-2}$ |
| 5b        | $-5.01 \times 10^{-2}$ | $5.01 \times 10^{-2}$ |
| 5c        | $-5.13 \times 10^{-2}$ | $5.13 \times 10^{-2}$ |
| 5d        | $-4.75 \times 10^{-2}$ | $4.75 \times 10^{-2}$ |
| 5e        | $-5.22 \times 10^{-2}$ | $5.22 \times 10^{-2}$ |
| 5f        | $-4.95 \times 10^{-2}$ | $4.95 \times 10^{-2}$ |
In the synthesized compounds (5a–f), the para chloro-phenyl ring (p-CPR) acts as electron-withdrawing group and influences different substitutions on the NLO response were studied at the ortho position of phenyl ring. The ester group is not involved due to the resonance between the two oxygen atoms and the electrons are unable to delocalize inside the phenyl ring. When the electron donating groups are attached to the p-CPR, the electron push full mechanism is the operative one and a large \( \beta_o \) value is obtained. However, if the electron-withdrawing groups are attached to the p-CPR, then the electron push full mechanism is not operating and the small \( \beta_o \) value is obtained in that case. The compound 5c has a strong electron donating group (MeS-) at the para position of the phenyl ring and we noticed a large \( \beta_o \) value (1373.76 au) for it according to the push full mechanism. The lower \( \beta_o \) value (218.51 au) was observed for compound 5f where an electron-withdrawing chloro group (Cl) is present on the para position of the phenyl ring. On both sides of the phenyl rings, similar chloro-groups are attached which make these rings strongly electron-withdrawing, and the net effect is zero. The moderate electron donating methoxy group at the para position of the phenyl ring (in 5e) had a reasonable NLO response compared to compound 5b where the acetate group has an internal resonance, which has a negative impact on the NLO response. The \( \beta_o \) values of 5e and 5b compounds were 954.47 au and 284.34 au, respectively. Compounds 5a and 5d had almost comparable \( \beta_o \) values (in the range of 510 au to 550 au). The reason may be that the presence of halogen groups on the meta and para positions of the ring nullified the effects of each other and the phenyl ring acted as moderately electron-donating. Based on these results, we suggest that compound 5c shows a better NLO response and can be used as an active NLO material in the future.

The hyperpolarizability of these compounds (5a–f) was also supported by the polarizability values (Table 5). Polarizability is defined as the electronic density distribution in a system. In compounds where electron-accepting and electron-donating groups are present at the opposite termini of the phenyl rings, they must have positive and negative centers and their \( \alpha_o \) is high. In contrast, in those compounds where both termini have similar functional groups, there is an equal distribution of electronic density and \( \alpha_o \) is low. For example, compound 5c had a high \( \alpha_o \) value (264 au) whereas 5f had a low \( \alpha_o \) value (235 au). The rest of the compounds had moderate values of \( \alpha_o \) in the range of 236 au to 252 au.

| Compounds | CAM-B3LYP | LC-BLYP |
|-----------|-----------|---------|
| \( \alpha_o \) | \( \beta_o \) | \( \alpha_o \) | \( \beta_o \) |
| 5a        | 236       | 515.43  | 229     | 436.87   |
| 5b        | 252       | 284.34  | 244     | 223.17   |
| 5c        | 264       | 1373.76 | 255     | 1010.54  |
| 5d        | 250       | 539.03  | 243     | 445.12   |
| 5e        | 244       | 954.47  | 237     | 776.21   |
| 5f        | 235       | 218.51  | 228     | 173.78   |

Table 5. Polarizability (\( \alpha_o \)) and hyperpolarizability (\( \beta_o \)) of compounds 5a–f with CAM-B3LYP and LC-BLYP methods.

Non-linear Refractive Index (\( n_2 \))

The quadratic non-linear refractive index (\( n_2 \)) was calculated by using degenerated four waves mixing gamma values (\( \gamma^{DFWM} (\omega) = (-\omega; \omega, -\omega, \omega) \)) as proposed by Tarazker et al. [30] and it is mathematically expressed as follows:

\[
\gamma^{DFWM} (-\omega; \omega, -\omega, \omega) = \frac{1}{3} \gamma (-2\omega; \omega, \omega, 0) + \frac{1}{3} \gamma (-\omega; \omega, 0, 0) + \frac{1}{3} \gamma (0; 0, 0, 0)
\]  

(5)
where \( \gamma (0; 0, 0, 0) \), \( \gamma (\omega; \omega, 0, 0) \), and \( \gamma (-\omega; \omega, \omega, 0) \) represent static, dc-Kerr, and EFSHG second hyperpolarizability coefficients, respectively. The \( \gamma^\text{DFWM} \) is further used to measure the quadratic non-linear refractive index \( (n_2) \) using Equation 6.

\[
n_2 (\text{cm}^2/\text{W}) = 8.28 \times 10^{-23} \gamma^\text{DFWM} \text{ (au)}
\]

The \( n_2 \) values of all compounds (5a–f) at various frequencies (0, 532 and 1064 nm) are given in Table 6 and graphically represented in Figure 2. In the spectral curves of \( n_2 \), the ESHG effect and dc-Kerr effect are similar and demonstrate the dominant contribution of both these effects in enhancing \( n_2 \) (Figure 3). However, the effect of the ESHG effect is more pronounced as compared to that of the dc-Kerr effect. The \( n_2 \) values for compounds (5a–f) were in the range \( 8.01 \times 10^{-18} \text{ au} \) to \( 9.46 \times 10^{-16} \text{ au} \) at \( \omega = 532 \text{nm} \). These compounds have \( n_2 \) values in the range \( 4.43 \times 10^{-18} \text{ au} \) to \( 8.41 \times 10^{-18} \text{ au} \) at \( \omega = 1064 \text{ nm} \). Among all compounds, the distinct effect was noticed at a low wavelength (532 nm) where the highest value \( (9.46 \times 10^{-16} \text{ au}) \) was noticed for compound 5c. These \( n_2 \) values proved the influence of various wavelengths on the amplitude of hyperpolarizability and gamma values of these compounds. Besides the various wavelengths, the structure of the compounds also plays a substantial role in the fluctuation of the NLO response. The structure of compound 5c has electron donating and electron withdrawing groups on both terminals of the main skeleton and an excellent push–pull mechanism occurs due to extended conjugation, and its NLO response is outstanding. This result is also supported by the nonlinear refractive index results.

Table 6. The static, dc-Kerr effect, electric field-induced second harmonic generation coefficients (in au), and quadratic non-linear refractive index \( (n_2 = \text{cm}^2/\text{W}) \) at different wavelengths (in nm) for compounds (5a–f).

| Compounds | Frequency | \( \gamma(0; 0, 0, 0) \) | \( \gamma(-\omega; \omega, \omega, 0) \) | \( \gamma(-2\omega; \omega, \omega, 0) \) | \( n_2 \) |
|-----------|-----------|----------------|----------------|----------------|-----------|
| 5a        | 532       | 48741.5        | 64320.8        | 199529         | 8.63 \times 10^{-18} |
|           | 1064      |                | 51988.4        | 59645.3        | 4.43 \times 10^{-18} |
|           | 0         |                | 54142.2        |                |           |
| 5b        | 532       |                | 73258.1        | 293432         | 1.16 \times 10^{-17} |
|           | 1064      |                | 58215.3        | 67505.4        | 4.96 \times 10^{-18} |
|           | 0         |                | 86291.9        |                |           |
| 5c        | 532       |                | 141361         | 34064301       | 9.46 \times 10^{-16} |
|           | 1064      |                | 95936.8        | 122589         | 8.41 \times 10^{-18} |
|           | 0         |                | 57794.5        |                |           |
| 5d        | 532       |                | 78682.2        | 314130         | 1.24 \times 10^{-17} |
|           | 1064      |                | 61860          | 72208.8        | 5.3 \times 10^{-18} |
|           | 0         |                | 63232          |                |           |
| 5e        | 532       |                | 92924.8        | 1013010.1      | 3.23 \times 10^{-17} |
|           | 1064      |                | 69085.6        | 83451.7        | 5.96 \times 10^{-18} |
|           | 0         |                | 49285.2        |                |           |
| 5f        | 532       |                | 64440.9        | 176408         | 8.01 \times 10^{-18} |
|           | 1064      |                | 52669.5        | 60014.7        | 4.47 \times 10^{-18} |
1,4-dioxane and the flask’s mouth was closed with a Teflon septum. The reaction mixture was stirred for about 25–30 min under an inert argon atmosphere. Then, K3PO4 (2 equiv.) and aryl boronic acids and 2 mL distilled water were added and the reflux reaction continued under an inert argon atmosphere for 18–25 h at 80–90 °C. During the reaction, the estimation of the reaction was determined by a thin layer chromatography technique using TLC cards. When the reaction was completed, the reaction mixture was filtered using Whatman filter paper and the solvent was evaporated by a rotary evaporator. The separation and purification of the impure products were carried out using the column chromatography technique. The NMR spectroscopic technique was used to find out the structure of the desired compound [31].

2-Bromo-4-chlorophenol 2-bromobutanoate (3), yellow liquid, 1H-NMR: (600 MHz, CDCl3) δ 7.9 (d, J = 1.5 Hz, 1H), 7.50 (dd, J1 = 7.5 Hz, J2 = 1.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 4.29 (t, J = 7.1 Hz, 1H), 2.05–2.10 (m, 2H, Ar), 1.1 (t, J = 8.0 Hz, 3H). 13C-NMR (150 MHz, CDCl3) δ 10.1 (CH3), 24.1 (CH2), 42.7 (CH), 115.2 (C), 117.6 (CH), 121.3 (CH), 129.4 (CH), 139.5 (C), 145.5 (C), 170.2 (C). HR-ESI-MS: m/z Calcd for C10H9Br2ClO, [M]+ 353.8909; found 353.8945.

3. Materials and Methods

3.1. Procedure for Synthesis of 2-Bromo-4-chlorophenyl-2-bromobutyrate (3)

First, 2-Bromo-4-chlorophenol (1 g, 4.820 mmol), MeCN (30 mL), pyridine (0.775 mL, 9.63 mmol), and 2-bromobutryl bromide (0.64 mL, 5.3 mmol) were added to a 250 mL round bottom flask with a magnetic stirrer. The flask’s mouth was closed with a Teflon septum. The flask was put on the magnetic hot plate along with an isotherm to maintain the temperature of the reaction mixture at 0 °C. The progress of the reaction was estimated by thin layer chromatography analysis. After 1 h, the reaction was completed. The separation and purification of the desired product was carried out using the column chromatography technique. The NMR spectroscopic technique was used to find out the structure of the desired compound [31].

Figure 3. Graphical representations of dc-Kerr, ESHG coefficients, and refractive index for compounds (5a–f) at different wavelengths (532 and 1064 nm).
the column chromatography technique. 1H-NMR was used to find out the structure of the newly synthesized compounds [32].

3′-Dichloro-4′-fluoro-[1,1′-biphenyl]-2-yl 2-bromobutanoate (5a), white crystals, m.p. 247–248°C. 1H-NMR (600 MHz, CDCl₃) δ 8.04 (d, J = 1.8 Hz, 1H), 8.00 (d, J = 1.5 Hz, 1H), 7.55 (dd, J₁ = 1.6 Hz, J₂ = 7.7 Hz, 1H), 7.41 (dd, J₁ = 7.7 Hz, J₂ = 8.0 Hz 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.35 (m, 1H), 4.2 (t, J = 7.0 Hz, 1H), 2.11–2.17 (m, 2H, Ar), 1.11 (t, J = 7.5 Hz, 3H). 13C-NMR (150 MHz, CDCl₃) δ 10.2 (CH₃), 25.4 (CH₂), 42.7 (CH), 117.6 (CH), 122.4 (C), 125.6 (CH), 130.5 (CH), 131.6 (CH), 132.5 (CH), 133.2 (CH), 132.9 (C), 133.4 (C), 133.9 (C), 148.1 (C), 162.3 (C), 170.1 (C). HR-ESI-MS: m/z Calcd for C₁₆H₁₂BrCl₂FO₂, [M]+ 406.0722; found 406.0742.

3′-Acetoxy-5-chloro-[1,1′-biphenyl]-2-yl 2-bromobutanoate (5b), yellow crystals, m.p. 268–269°C. 1H-NMR (600 MHz, CDCl₃) δ 8.00 (d, J = 2.0 Hz, 1H), 7.50 (dd, J₁ = 7.9 Hz, J₂ = 1.8 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.42–7.34 (m, 2H), 7.35 (dd, J₁ = 7.7 Hz, J₂ = 1.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 4.20 (t, J = 7.0 Hz, 1H), 2.35 (s, 3H), 2.10–2.15 (m, 2H, Ar), 1.10 (t, J = 7.9 Hz, 3H). 13C-NMR (150 MHz, CDCl₃) δ 10.1 (CH₃), 19.4 (CH₃), 25.6 (CH₂), 45.4 (CH), 120.4 (CH), 121.1 (CH), 122.3 (CH), 128.7 (CH), 129.1 (CH), 131.2 (C), 132.7 (CH), 134.8 (CH), 136.3 (C), 137.5 (C), 145.1 (C), 148.1 (C), 170.1 (C), 171.2 (C). HR-ESI-MS: m/z Calcd for C₁₆H₁₆BrClO₄, [M]+ 411.6808; found 411.6892.

5-Chloro-4′-(methylthio)-[1,1′-biphenyl]-2-yl 2-bromobutanoate (5c), brown crystals, m.p. 250–251°C. 1H-NMR (600 MHz, CDCl₃) δ 8.00 (d, J = 1.9 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.35 (dd, J₁ = 7.5 Hz, J₂ = 2.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 4.19 (t, J = 7.0 Hz, 1H), 2.53 (s, 3H), 2.05–2.11 (m, 2H, Ar), 1.10 (t, J = 7.0 Hz, 3H). 13C-NMR (150 MHz, CDCl₃) δ 10.1 (CH₃), 19.4 (CH₃), 25.6 (CH₂), 45.4 (CH), 121.1 (CH), 124.3 (CH), 125.4 (2CH), 128.1 (C), 130.2 (CH), 131.1 (C), 132.7 (C), 134.8 (CH), 135.4 (CH), 136.1 (C), 146.1 (C), 170.1 (C). HR-ESI-MS: m/z Calcd for C₁₆H₁₆BrClO₂S, [M]+ 399.7145; found 399.7119.

3′,4′,5-Trichloro-[1,1′-biphenyl]-2-yl 2-bromobutanoate (5d), white crystals, m.p. 276–277°C. 1H-NMR (600 MHz, CDCl₃) δ 7.96 (d, J = 2.3 Hz, 1H), 7.83 (d, J = 1.9 Hz, 1H), 7.51–7.43 (m, 2H), 7.40 (dd, J₁ = 8.2 Hz, J₂ = 2.0 Hz, 1H), 7.33 (d, J = 1.5 Hz, 1H), 4.20 (t, J = 7.0 Hz, 1H), 2.15–2.20 (m, 2H, Ar), 1.10 (t, J = 8.0 Hz, 3H). 13C-NMR (150 MHz, CDCl₃) δ 10.1 (CH₃), 25.6 (CH₂), 45.4 (CH), 121.1 (CH), 126.5 (CH), 128.1 (CH), 130.2 (CH), 131.2 (CH), 132.7 (C), 135.8 (CH), 136.2 (C), 137.2 (C), 138.5 (C), 141.5 (C), 148.1 (C), 170.1 (C). HR-ESI-MS: m/z Calcd for C₁₆H₁₂BrCl₃O₂, [M]+ 422.5233; found 422.5289.

5-Chloro-4′-methoxy-[1,1′-biphenyl]-2-yl 2-bromobutanoate (5e), light brown crystal, m.p. 237–238°C. 1H-NMR (600 MHz, CDCl₃) δ 7.98 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.5 Hz, 2H), 7.49–7.35 (m, 2H), 7.10 (dd, J₁ = 8.2 Hz, J₂ = 1.5 Hz, 2H), 4.22 (t, J = 6.9 Hz, 1H), 3.93 (s, 3H), 2.08–2.15 (m, 2H, Ar), 1.10 (t, J = 8.0 Hz, 3H). 13C-NMR (150 MHz, CDCl₃) δ 10.1 (CH₃), 25.6 (CH₂), 45.4 (CH), 60.2 (CH₃), 116.1 (CH), 116.5 (CH), 124.5 (CH), 125.3 (C), 128.4 (CH), 130.3 (CH), 131.4 (C), 132.2 (CH), 133.3 (CH), 132.7 (C), 135.8 (C), 151.2 (C), 170.1 (C). HR-ESI-MS: m/z Calcd for C₁₇H₁₈BrClO₃S, [M]+ 383.4515; found 383.4565.

3′,5-Dichloro-[1,1′-biphenyl]-2-yl 2-bromobutanoate (5f), white crystal, m.p. 232–233°C. 1H-NMR (600 MHz, CDCl₃) δ 8.01 (d, J = 2.5 Hz, 2H), 7.52 (dd, J₁ = 7.5 Hz, J₂ = 1.9 Hz, 1H), 7.55 (t, J = 2.0 Hz, 1H), 7.42–7.41 (m, 2H), 7.34 (d, J = 7.0 Hz, 1H), 4.22 (t, J = 7.0 Hz, 1H), 2.08–2.15 (m, 2H, Ar), 1.10 (t, J = 8.0 Hz, 3H). 13C-NMR (150 MHz, CDCl₃) δ 10.1 (CH₃), 25.6 (CH₂), 45.4 (CH), 121.1 (2CH), 122.4 (CH), 121.9 (CH), 125.2 (CH), 128.7 (2CH), 130.2 (C), 132.7 (C), 133.2 (C), 134.7 (C), 151.3 (C), 171.2 (C). HR-ESI-MS: m/z Calcd for C₁₆H₁₃BrCl₂O₂, [M]+ 388.0861; found 388.0839.

3.3. Computational Details

All calculations were performed in Gaussian 09 software [33]. The optimized structures were drawn using Gauss View 5.0 software [34]. The structures of synthesized compounds (5a–f) were optimized with the hybrid functional (B3LYP) of the density functional theory (DFT). B3LYP is a widely used functional for the optimization of organic molecules because the minimization of errors
in the geometrical parameters is lower for B3LYP compared to that of other density functionals. The split valence basis set developed by Pople’6-311G (d,p) was implemented for molecular orbital descriptions. For further confirmation of these minimum energy structures obtained from optimization (Figure 1), frequency analysis and frontier molecular orbital analysis were done at the same level of theory. During frequency simulations, the harmonic force constant was calculated, which validated the absence of imaginary frequency and justified these as true minima structures. FMOs, reactivity descriptor parameters (ionization potential, electron affinity, chemical hardness, electrophilicity index, electronic chemical potential, and nucleophilicity), and molecular electrostatic potential (MEP) were calculated with the B3LYP/6-311G (d,p) method. NLO properties including polarizabilities, first hyperpolarizability, and gamma values were calculated with CAM-B3LYP and LC-BLYP with 6-311+G (d,p) levels. The best NLO results were obtained by the CAM-B3LYP/6-31+G (d,p) level, so we discussed our results obtained on this level of theory. The nonlinear refractive index was also calculated a with the CAM-B3LYP/6-31+G (d,p) method.

4. Conclusions

In conclusion, a series of 2-bromo-4-chlorophenyl-2-bromobutyrate derivatives (5a–f) were synthesized and frontier molecular orbitals (FMOs) and molecular electrostatic potential (MEP) analysis were done. FMOs analysis revealed that among all the derivatives, 5c is most reactive, having a HOMO–LUMO band gap of 4.27 eV, whereas the HOMO–LUMO band-gap for 5f was 5.19 eV, and was the most stable. The chemical hardness of 5f displayed the highest value (2.60 eV), whereas 5c has the lowest value and was chemically soft and reactive. Among all the newly synthesized compounds, 5d displayed the highest chemical potential value. The molecular electrostatic potential (MEP) investigation gave us the idea of electrophilicity and nucleophilicity of the synthesized compounds, and it was envisaged that depression of electron density is highly dependent on the substituent present on an aromatic ring. The first hyperpolarizability values showed that all synthesized derivatives has a potential non-linear optics (NLO) response, but 5c has a significant NLO potential due to its large βo (1373.76 au) value.

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