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Synthesis of 1-isopropyl-4,7-dimethyl-3-nitronaphthalene: An experimental and theoretical study of regiospecific nitration

N. Ourhriss[1,4], A. Zeroual[1,2], M. Ait Elhad[1], N. Mazoir[1,3], A. Abourriche[4], C. A. Gadhi[5], A. Benharref[1], A. El Hajbi[2]

[1] *Laboratory of Biomolecular Chemistry, Natural Substances and Reactivity, URAC 16, Faculty of Sciences Semlalia, Cadi Ayyad University, P.O. Box 2390, Marrakech, Morocco*
[2] *Laboratory of Physical Chemistry, Faculty of Science, Chouaïb Doukkali University, P.O. Box 20, 24000 El Jadida, Morocco*
[3] *Department of Chemistry, Faculty of Sciences El Jadida, Chouaib Doukkali University, P.O. Box 20, 24000 El Jadida, Morocco*
[4] *Biomolecular and Organic Synthesis Laboratory, Faculty of Sciences Ben M'sik Casablanca, Hassan II University, Morocco*
[5] *Laboratory of Biotechnology, Valorization and Protection of Vegetable Resources (Biote V.R.V), Faculty of Sciences Semlalia, Cadi Ayyad University, P.O. Box 2390, Marrakech, Morocco*

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- ✓ DFT/6-31(d,p)

zeroual19@yahoo.fr
Phone: +212667845405

Abstract

In this work, we were able to achieve a total regioselectivity for the nitration at C3 position of 1-isopropyl-4,7-dimethylnaphthalene. The structures of the nitro isomers obtained were established by ^{1}H, ^{13}C NMR spectroscopy and confirmed using single-crystal X-Ray diffraction. In parallel, a computational study has been performed in agreement with the experimental results obtained. With this purpose, all the σ-complexes of the five nitro isomers neutral and protonated were optimized both in gas phase by using the B3LYP/6-31(d,p) level of computational theory.

1. Introduction

The aromatic nitration is particularly an electrophilic aromatic substitution (EAS) in which a hydrogen atom of the aromatic ring is substituted by a nitro group ($-NO_2$) to form nitrobenzene. The aromatic nitro compounds are of huge industrial importance in synthesis of pharmaceutical drugs [1, 2], polymers and perfumes [3], and for the synthesis of other important chemicals compounds like as amine and isocyanate functionality [4, 5]. However, the early research into aromatic nitration was fuelled exclusively by their use as explosives and intermediates in the synthesis of alkaloid compounds [6].

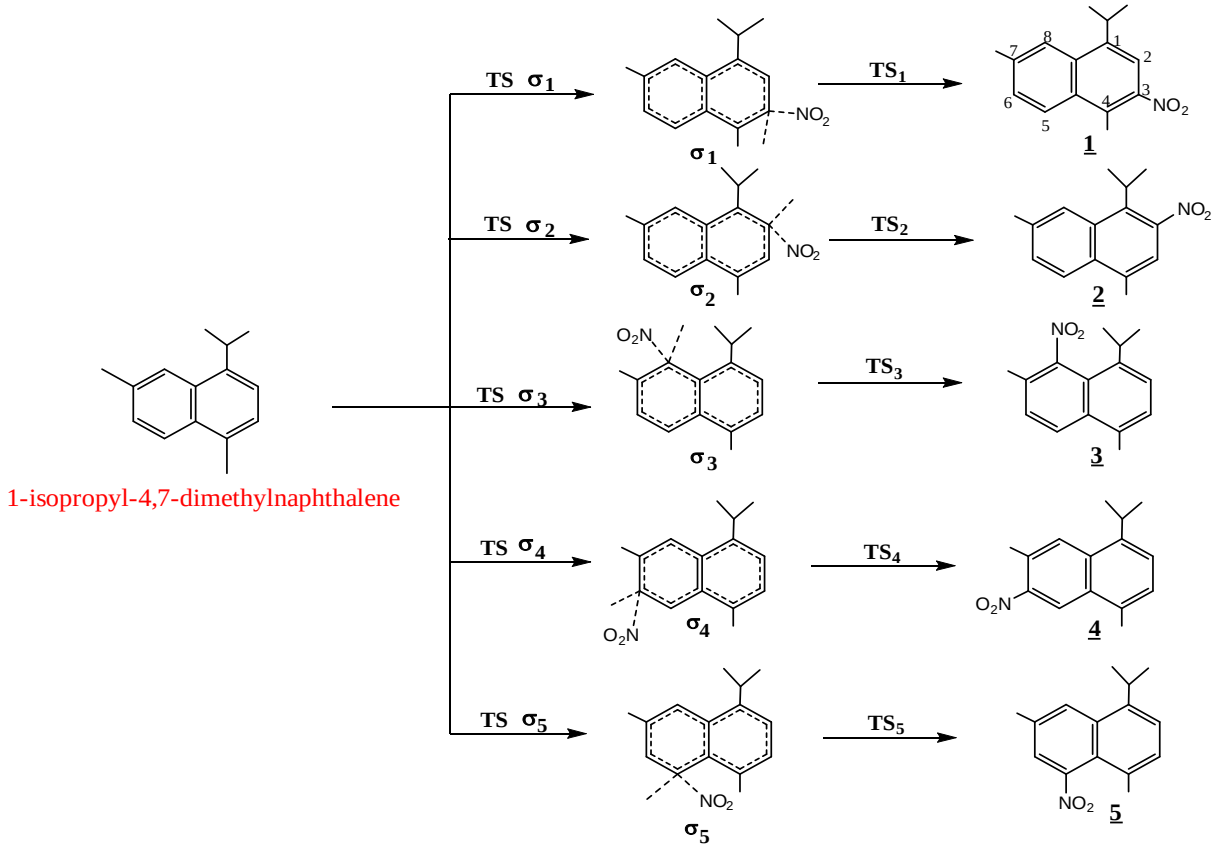
Extending our previous work, for the synthesis of new nitrobenzene: 1-isopropyl-4,7-dimethyl-3-nitronaphthalene (1) using treatment of 1-isopropyl-4,7-dimethylnaphthalene (scheme 1), hemisynthesized from Cedrus atlantica essential oil and nitric acid (1eq). The reaction was regiospecific and the structures of the obtained products were analyzed by NMR spectroscopy and confirmed using single crystal X-ray diffraction [7]. In the present contribution, we present an efficient theoretical calculations at the DFT/B3LYP/6–31(d,p) level to provide a better understanding of this regiospecificity.

2. Experimental

2.1. *General procedure for the nitration of aromatic compound*

In a reactor of 250 ml equipped with a magnetic stirrer and a dropping funnel, we introduced 60 ml of dichloromethane, 3 ml of nitric acid and 5 ml of concentrated sulfuric acid. After cooling, added dropwise through the dropping funnel 6 g (30 mmol) of 1-isopropyl-4,7-dimethylnaphthalene dissolved in 30 ml of dichloromethane. The reaction mixture was stirred for 4 h, then added 50 ml of water ice and extracted with dichloromethane. The organic layers were combined, washed five times with 40 ml with water and dried over sodium sulfate and then concentrated under vacuum. The residue was subjected to chromatography on a column

of silica gel with hexane-ethyl acetate (98/2) as eluent, to obtain 2.86 g (20 mmol) of the title compound which was recrystallized in hexane (the yield of obtained: 67%).



Scheme 1. Competitive regio-isomeric pathways associated with EAS reaction of 1-isopropyl-4,7-dimethylnaphthalene and nitric acid.

1-isopropyl-4,7-dimethyl-3-nitronaphthalene.
Colorless crystal, ^{1}H NMR ($CDCl_3$, 300 MHz) : 7.78 (1H, s, H-2), 7.38 (1H, d, J = 7.0 Hz, H-5), 7.94 (1H, d, J = 7 Hz, H-6), 7.71 (1H, s, H-8), 2.65 (3H, s, H-9), 2.46 (3H, s, H-10), 3.12 (1H, sept, J = 7.0 Hz, H-11), 1.42 (3H, d, H-12), 1.41 (3H, d, H-13). ^{13}C NMR ($CDCl_3$, 300 MHz) : 139.8 (C-1), 120.3 (C-2), 145.8 (C-3), 128.1.4 (C-4), 129 (C-4a), 125.3 (C-5), 129.2 (C-6), 138.7 (C-7), 125.4 (C-8), 132.5 (C-8a), 21.8 (C-9), 18.6 (C-10), 28.8 (C-11), 23.7 (C-12), 23.8 (C-13).

2.2 *Material and methods*
All calculations reported in this work were performed in the GAUSSIAN 09 [8], B3LYP/6-31G(d,p) [9] as well as theoretical levels were performed. Optimizations of the stable structures were performed with the Berny algorithm, whereas the transition states were calculated using the QST2 [10] procedure followed by the TS method. Stationary points were characterized by frequency calculations. All transition states showed only one negative Eigen value in their Hessian matrices. The global electrophilicity index [11] ω, was given by the following expression, $\omega = \frac{\mu^2}{2\eta}$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities could be approached in terms of the one-electron energies toward the frontier molecular orbital HOMO and LUMO as $\mu = \frac{\varepsilon_{HOMO} - \varepsilon_{LUMO}}{2}$ and $\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO}$, respectively. [12] The empirical nucleophilicity index N, [13] based on the HOMO energies obtained within the Kohn–Sham scheme, [14] and defined as $N = \varepsilon_{HOMO}(\text{Nu}) - \varepsilon_{HOMO}(\text{TCE})$. The nucleophilicity was referred to tetracyanoethylene (TCE). Electrophylic and nucleophilic Parr functions, [15-22] were obtained through the analysis of the Mulliken Atomic Spin Density (ASD) of the radical anion and radial cation of the reagents. The local electrophilicity and nucleophilicity indices were evaluated using the following expressions: $\omega_K = \omega.P_k^+$, $N_K = N.P_k^-$.

3. **Results and discussion**

3.1. *DFT analysis based on the global and local reactivity indexes*

The global indices, named electronic chemical potential μ, chemical hardness η, global electrophilicity ω and global nucleophilicity N, for the reagents are summarized in Table 1.

Table 1: DFT/B3LYP/6-31G (d,p) Electronic chemical potential μ, chemical hardness η, electrophilicity ω, and nucleophilicity N values, in eV.

	μ	η	N	ω
1-Isopropyl-4,7-dimethylnaphthalene (**1**)	-3.12	4.62	4.09	1.05
Nitro	-5.17	5.99	1.35	2.23

The electronic chemical potential of Nitro, μ = -5.17 eV, was lower than 1-isopropyl-4,7-dimethylnaphthalene, μ = -3.12 eV, indicating that the global electron density transfer (GEDT) along the corresponding reactions will flux from the starting material, toward the nitro. It was also clear from thetable 1 that the nitro presented a high electrophilicity index, w = 2.23 eV, being classified as an electrophile and a very low nucleophilicity N index, N = 1.35 eV. On the other hand, 1-isopropyl-4,7-dimethylnaphthalene presented a very low electrophilicity, w = 1.05 eV and nucleophilicity indices, N= 4.09 eV. The high electrophilic character of nitro allowed the participation of the starting material as nucleophile.

The most favorable reactive channel was that involving the initial two-centre interactions between the most electrophilic P_k^+ and nucleophilic P_k^- Parr functions centre of both reagents

Recently, electrophilic P_k^+ and nucleophilic P_k^- Parr functions have been proposed to analyse the local reactivity in polar processes involving reactions between a nucleophile-electrophile pair.

The analysis of the nucleophilic P_k^- Parr functions of 1-isopropyl-4,7-dimethylnaphthalene,showed that the C3 carbon presented the maximum values of P_k^-: 0.23, (Fig. 1) indicating that this site is the most nucleophilic centers. Consequently, the regioselectivity observed was predicted correctly by the Parr function.

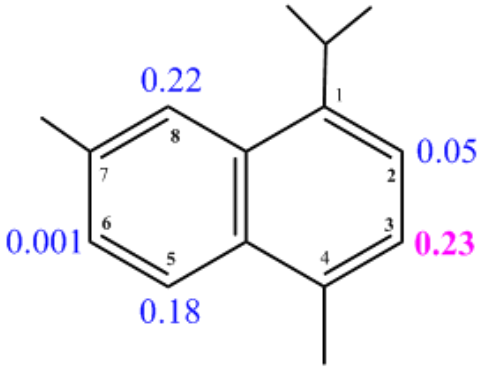


Figure 1: Nucleophilic P_k^- Parr functions of 1-isopropyl-4,7-dimethylnaphthalene.

3.2. Kinetic study

In order to show that the nitration preferentially attacked on the C3 position, we calculated the energies of the reactants, the products and the transition states energies. Table 2 summarized the total and the relative energies for the EAS reaction of 1-isopropyl-4,7-dimethylnaphthalene.

In order to understand and interpret the regioselectivity observed in nitration aromatic substitution of the starting material, PES of the reaction was calculated by B3LYP/6-31G(d,p) method. Intrinsic Reaction Coordinate (IRC) calculations were performed to characterize the transition states on the PES (Fig. 2).

We can observed from figure 2 that the activation energies of σ-complexes are 60.69, 73.50, 69.92, 73.52 and 79.52 for TS- σ1, TS- σ2, TS- σ3, TS- σ4 and TS- σ5 respectively, showing that the formation of σ- complexes 1, isomers was kinetically preferred.

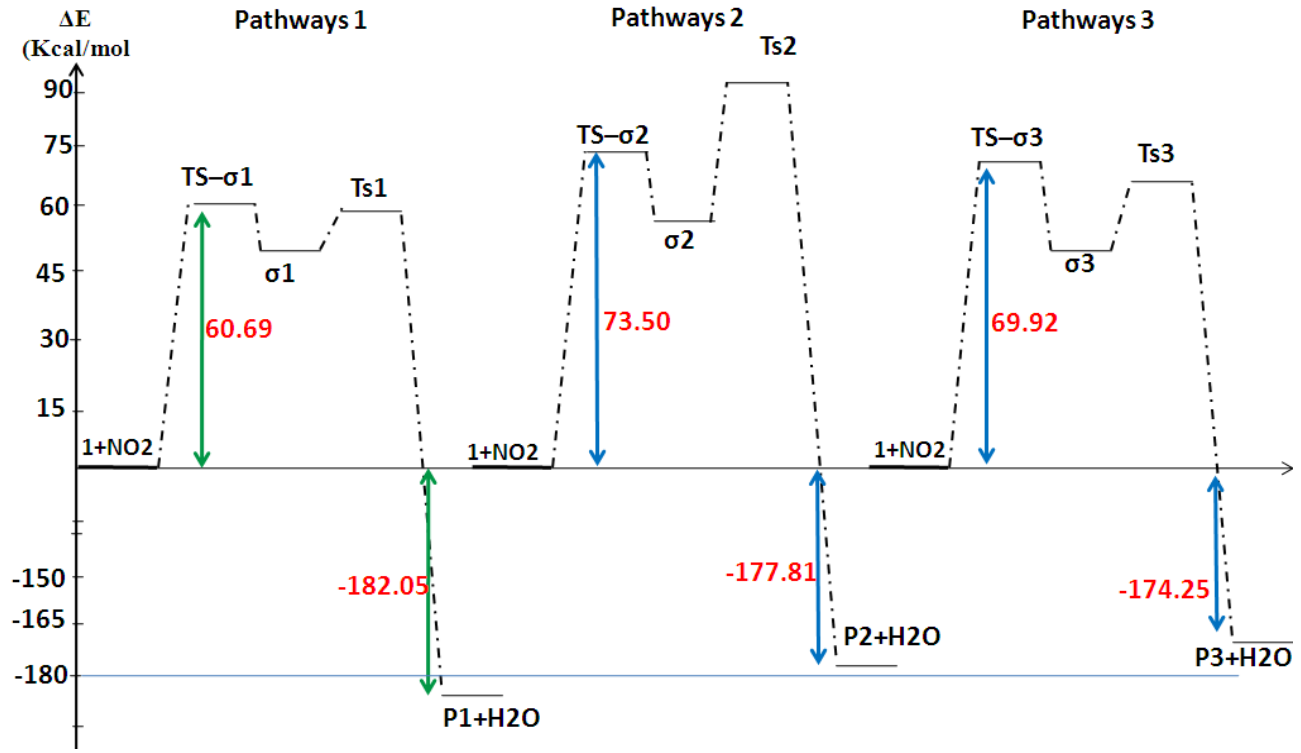
According to the results of both methods, TS1 transition state was more stable than anther TSs transition (TS2, TS3, TS4 and TS5 (Table 2). In the other hand, the reaction energies of the complex σ-1 were more stable than complexes σ-2, σ-3, σ-4 and σ-5.

Table 2 and figure 2 indicated that, the reaction energies of the product P1 were more stable than P2, P3, P4 and P5 imply that formation of the corresponding formal electrophilic aromatic substitution was highly exothermic by 182.05, 177.81, 174.25, 181.14 and 145.81 kcal mol-1. These values clearly indicated that the product P1 was thermodynamically preferred in clears agreement with experimental results.

Table 2: B3LYP/6-31G(d) energies E (in a.u.) and relative energies (ΔE, in kcal/mol) of the reagents, transition states and products.

System	E	ΔE
Reagents	-863.1485	--------
TS–σ1	-863.0518	60.69
TS–σ2	-863.0314	73.50
TS–σ3	-863.0371	69.92
TS–σ4	-863.0313	73.52
TS–σ5	-863.0219	79.43
σ1	-863.0666	51,40
σ2	-863.0554	58.40
σ3	-863.0682	50.39
σ4	-863.0555	58.35
σ5	-863.0570	57.44
T1	-863,0081	59.10
T2	-863.0066	92.79
T3	-863.0444	65.32
T4	-862.9985	94.14
T5	-863.0173	82.35
P1+ H_2O	-863.4386	-182.05
P2+ H_2O	-863.4319	-177.81
P3+ H_2O	-863.4262	-174.25
P4+ H_2O	-863.4372	-181.14
P5+ H_2O	-863.3809	-145.81

Relative to 1-isopropyl-4,7-dimethylnaphthalene + HNO_3



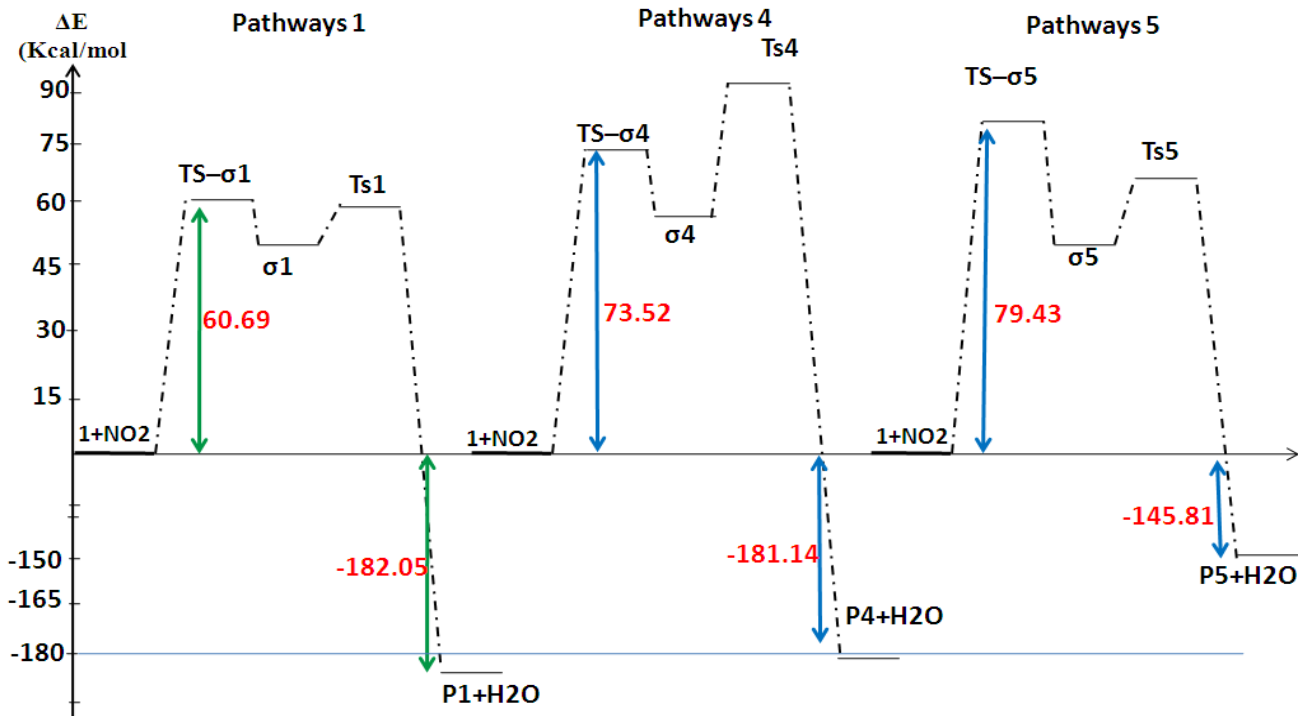


Figure 2: Pathways for nitration aromatic substitution reactions of 1-isopropyl-4,7-dimethylnaphthalene

The optimized geometries of the TSs involved in the studied nitration aromatic substitution reactions of starting material and distances of the forming bonds were presented in Fig. 3.

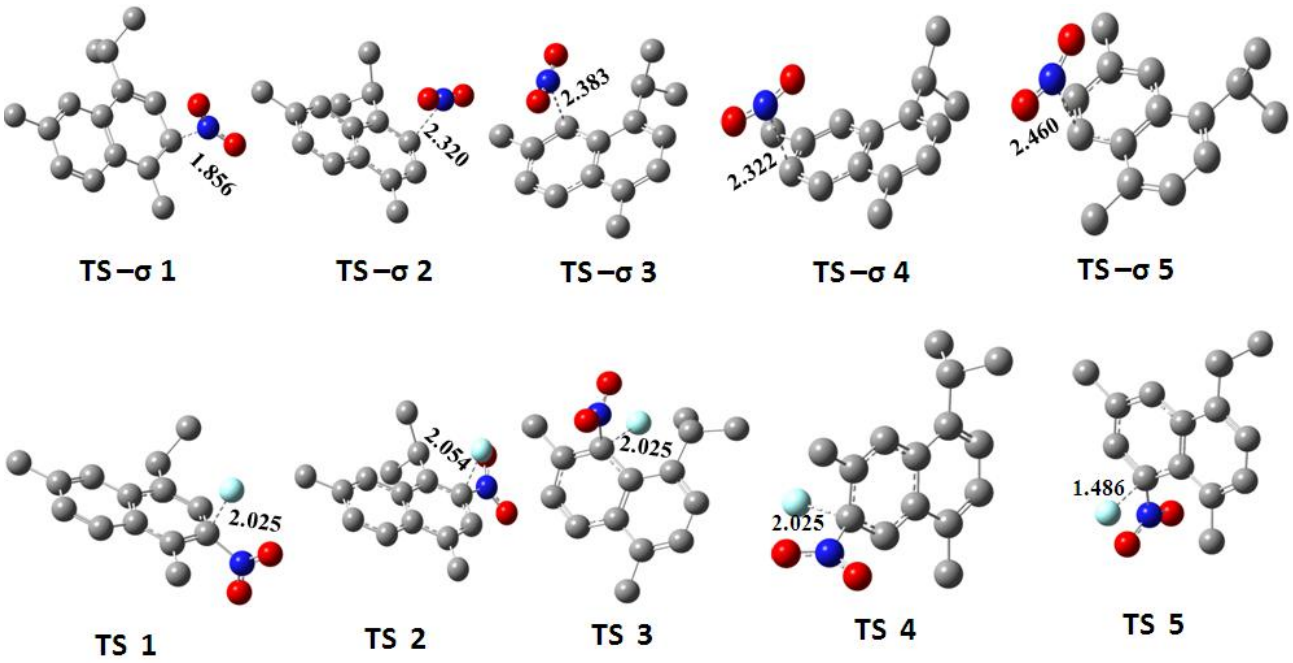


Figure 3: Optimized TS involved in the nitration aromatic substitution reactions of 1-isopropyl-4,7-dimethylnaphthalene and the bonds in (Å).

The lengths of the N-C bonds at the TSs are 1.856 at TS- σ1, 2.320 A at TS- σ2, 2.383 at TS- σ3, 2.322 at TS- σ4 and 2.460 A at TS- σ5. The N-C bond in the TSs associated with the most favorable P1 channels was shorter than the N-C one. These geometric parameters suggested an asynchronous bond formation process along the most favorable P1 regioisomer.

Conclusions

This study showed that the 1-isopropyl-4,7-dimethyl-3-nitronaphthalene could be easily synthesized via the nitration aromatic substitution reactions of 1-isopropyl-4,7-dimethylnaphthalene under a very mild conditions and in short reaction time. Finally, a DFT study of the mechanism and regioselectivity showed that the analysis of relative energies of all species involved in the nitration aromatic substitution reactions was kinetically and thermodynamically favorable. In addition, DFT energies indicated that the nitration aromatic substitution reaction was completely regioselective.

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