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Short Note

4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-2-nitrobenzamide

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Abstract: As part of our ongoing attempt to broaden the applications of the amidoxime moiety as a potential source of new antileishmanial agents, this study focuses on the product 4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-2-nitrobenzamide. This unexpected amide was obtained in an 85% yield as the major product with a conventional amidoxime synthesis protocol (Ethanol/Na_2CO_3) involving the reaction of hydroxylamine and a nitrile group. The formation of this amide derivative instead of the expected amidoxime can be attributed to two complementary effects: the strong electron effect of the nitro group and the influence of ethanol, a polar protic solvent. Alternatively, the desired amidoxime derivative, 4-(5-benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-*N*′-hydroxy-2-nitrobenzimidamide, was obtained in an 80% yield by an alternative protocol (DMSO/KO*t*Bu). This original compound, featuring a nitro group in the ortho position to the amidoxime, will be further evaluated, both in the field of medicinal chemistry and in other relevant areas, highlighting an unusual method to access amidoximes from hindered substrates.

Keywords: amidoxime; amide; 4,5-dihydrofuran; nitro group; leishmania

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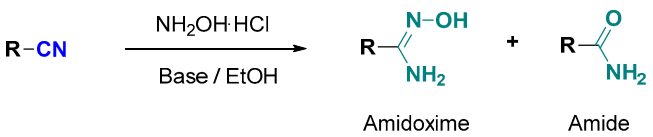
1. Introduction

Amidoxime is a functional group extensively studied for environmental applications, for example in the treatment of seawater or wastewater [1–3]. The growing number of citations and publications over time indicates significant interest, which extends to other fields such as polymer science, organic chemistry and medicinal chemistry [4–8]. Our team has previously reported the antileishmanial activity of some original compounds bearing a dihydrofuran and an amidoxime group [9,10].

The amidoxime group is usually obtained by reacting hydroxylamine (released in situ from its hydrochloride salt in a protic solvent: ethanol or methanol) with nitriles under basic conditions, usually involving $CaCO_3$ or Na_2CO_3, (Scheme 1). The desired amidoxime formation is often accompanied by the corresponding amide byproduct, which can vary in yield. In certain cases, the formation of amide is not reported, which could be a result of methods that achieved yields reaching as much as 100% [11].



Scheme 1. Traditional amidoxime synthesis.

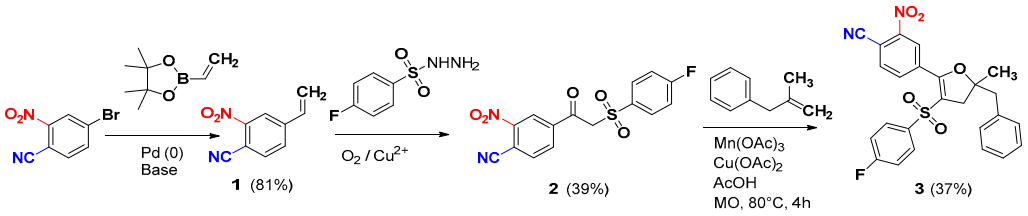
Other synthetic methods, such as the reaction of hydroxylamine with iminoethers or amidine hydrochlorides, as well as the reduction of oxyamidoximes or nitrosolic acids, are limited in their operations or used under specific conditions [12–16]. Less common conditions involve KO*t*Bu in DMSO [17,18]. However, there is little available information about other aryl nitriles, particularly those bearing a nitro group in the ortho position to the nitrile function.

The literature survey revealed that the amidoxime formation reaction is limited to aryl-nitriles and to certain alkyl substrates, with a lack of information regarding more complex or sterically hindered electrophilic substrates. Although this reaction has been widely reported to be highly efficient, the scope of more diverse substrates remains to be clarified.

In this work, an unexpected amide product was obtained via a conventional amidoxime protocol from an aryl nitrile substrate. Notably, the distinctive feature of the starting material, in this case, was the presence of a nitro group in the ortho position to the cyano group.

2. Results

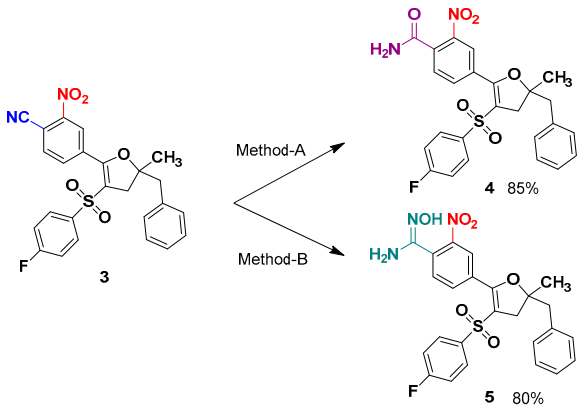
A three-step synthesis was performed to access the aryl nitrile **3** bearing a nitro group in the ortho position, serving as the substrate to obtain the amidoxime derivative **5** (Scheme 2). To achieve this synthesis, a vinyl intermediate was synthesized, compound **1**, (81% of yield) through a cross-coupling Suzuki–Miyaura reaction with 4-bromo-2-nitrobenzonitrile as the starting material. Subsequently, compound **1** was converted to a linear β-ketosulphone **2** through a radical reaction, and the appropriate hydrazine, in a 39% yield. A subsequent oxidative radical cyclization step mediated by $Mn(OAc)_3$ led to the 4,5-dihydrofuran scaffold **3** in a moderate yield (37%).



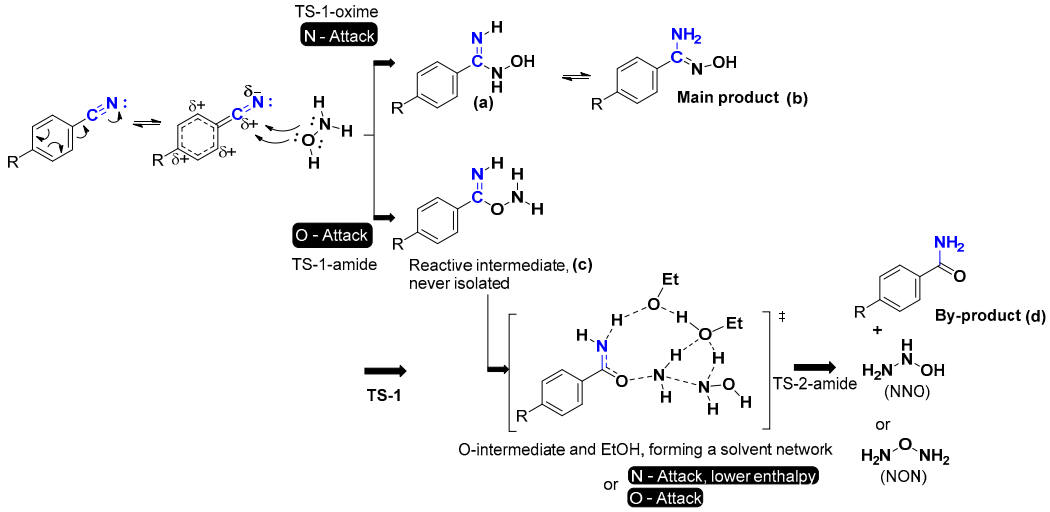
Scheme 2. Synthesis of an aryl nitrile substrate bearing a nitro group in the ortho position.

In an attempt to obtain the amidoxime **5**, the latter compound **3** was subjected to a microwave assisted reaction following method (A) (Scheme 3). Surprisingly, the structure of the major product obtained (with an 85% yield) was identified and confirmed by HRMS to be of the amide derivative 4-(5-benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-2-nitrobenzamide. Based on this result, it was hypothesized that the formation of the amide could come from interactions between ethanol and hydroxylamine, as the solvation effect could modify the nucleophilic character of the hydroxylamine. Their ambident behavior (O- or N-attack) has been documented for other substrates [19–21]. Taking this into consideration, an alternative solvent DMSO was used (method B, Scheme 3), giving the amidoxime **5** in an 80% yield (method B, Scheme 3).

Plausible mechanistic explanations have been suggested by Srivastava et al. [22] and Stephenson et al. [23], as shown in Scheme 4, considering the ambident nucleophile nature of NH_2OH (O and N atoms possessing sharply different nucleophilicities) the N-attack and the O-attack ways have been highlighted. In the case of an N-attack over the carbon atom of the nitrile, the amidoxime formation could be favored (compound b) via *N*-hydroxybenzimidamide (compound a, Scheme 4). Moreover, with an O-attack type, the amide formation may be favored with the attack of a second equivalent of hydroxylamine (by the oxygen or nitrogen) and the subsequent formation of the O-aminohydroxylamine (NON) or the hydroxyhydrazine (NNO).



Scheme 3. Influence of the reaction conditions on the amide and the amidoxime synthesis. Method-A: 4 equiv. $NH_2OH\cdot HCl$, 2 equiv. Na_2CO_3, EtOH, N_2, 90 °C, MW, 1 h. Method-B: 10 equiv. $NH_2OH\cdot HCl$, 10 equiv. KO*t*Bu, DMSO, N_2, 0 °C to RT, 18 h.

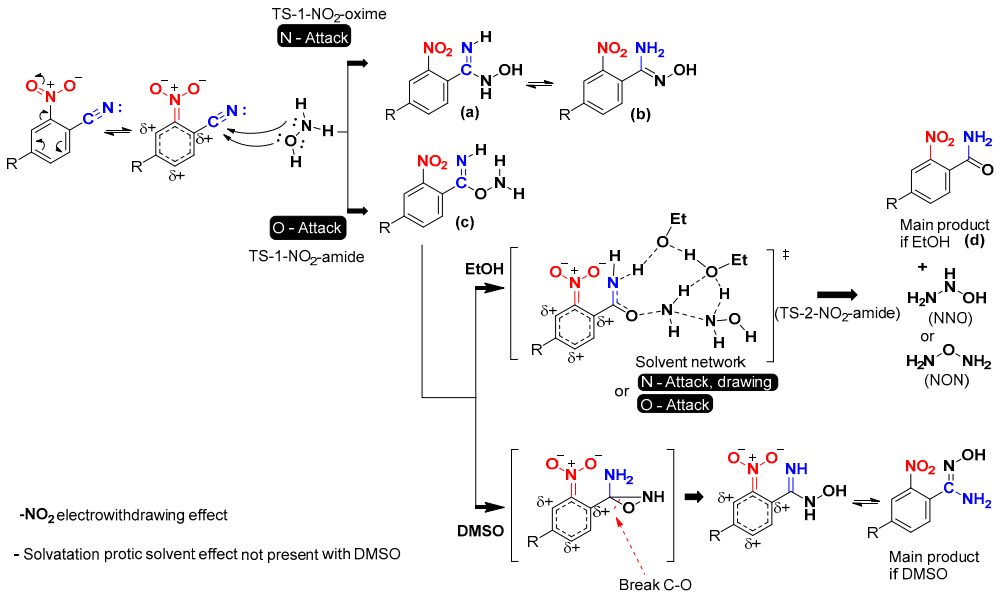


Scheme 4. Reaction mechanisms of the reaction between nitriles and hydroxylamine.

Vörös et al. reported a theoretical and experimental analysis to describe the byproduct formation (not as the main product) of the amide [24,25]. This mechanism depends on the energetic requirement for two types of solvents, a protic type vs. ionic liquids. According to their thermodynamic analysis, in a protic solvent as ethanol, the transformation of intermediate **c** into the amide byproduct **d** exhibits a transition state (TS-2-amide) with a lower enthalpy than the transition state of the formation of compound **a** (TS-1-oxime), as shown in Scheme 4. Likewise, the enthalpy difference between the two transition states, TS-1-oxime and TS-2-amide varies with the solvent with TS-1-oxime > TS-2-amide in a protic solvent like ethanol, but inverted to TS-2-amide > TS-1-oxime with an ionic solvent. Therefore, the reaction conditions favoring a more stable TS-2-amide might then explain the byproduct formation of the amide [24,25].

Our results showed that a combined effect may be suggested to explain the formation of an amide as the main product. Notably, we observed that substrates without a nitro group predominantly form amidoxime in both DMSO and ethanol conditions. However, when a nitro group is introduced in ortho position to the nitrile function, in a protic solvent such as ethanol, this predominantly gives the amide product, while DMSO demonstrates a more specific tendency towards amidoxime formation. These observations suggest the next plausible theoretical approaches considering both the mechanistic insights reported by Vörös et al. and the theory of 'hard and soft' nucleophiles and electrophiles [26,27]. Specifically, the predominant formation of the amide derivative as the main product using ethanol

as a solvent could be related to the more stable transition state O-intermediate-to-amide (TS-2-NO_2-amide), Scheme 5. This enhanced stability could be influenced by both the electronic influence of the nitro group and the solvation effect of the ethanol (where hydrogen bond interactions occur) forming a solvent network that could mediate the proton transfer in the course of the reaction [28]. Furthermore, regarding the inductive and mesomeric effects of the nitro group [29,30], the nitrile becomes a more electrophilic center, and therefore a 'harder' electrophile that predominantly undergoes an O-attack from the hydroxylamine in TS-1, since 'hard–hard' (and 'soft–soft') interactions are preferred [31,32]. Meanwhile, the predominant formation of amidoxime observed with DMSO as a solvent could be explained either by a hindered second hydroxylamine attack in the absence of an appropriate solvent network necessary to stabilize the TS-2; then, the intermediary compound **c** via TS-1 is unable to transform forward **d** and the process either turns back to an N-attack or to an alternative possibility involving a cyclic intermediate rearrangement [25].



Scheme 5. Theorical difference in the reaction mechanisms with an electron-withdrawing group.

3. Materials and Methods

3.1. Chemistry

Reagents were purchased from Sigma-Aldrich (3050 Spruce Street St. Louis, MO, USA), Fluorochem (Unit 14 Graphite Way, Hadfield, Glossop SK13 1QH, UK), Fisher Scientific (168 3rd Ave, Waltham, MA, USA) or TCI chemicals (9211 North Harborgate Street, Portland, OR, USA), and used without further purification. Microwave reactions were performed using monomode reactors: Biotage Initiator® classic (Uppsala, Sweden) in sealed vials with output power ranging from 0 to 400 W. The following adsorbent was used for column chromatography: silica gel 60 (Merck KgaA, Darmstadt, Germany, particle size 0.063–0.200 mm, 70–230 mesh ASTM). Reaction monitoring of intermediary compounds was performed either using aluminum TLC plates (5 × 5 cm) with silica gel coated 60F-254 (Merck) in an appropriate eluent and visualized using ultraviolet light under a UV-Lamp VL-6.CL., at 254 nm (6 W) and 365 nm (6 W) or using an LC-MS apparatus, Thermo Scientific Accela High Speed LC System® coupled to a Thermo MSQ Plus® quadrupole mass spectrometer, with an HPLC column Thermo Hypersil Gold® (168 3rd Ave, Waltham, MA, USA) 50 × 2.1 mm (C18 bounded), with particles of a diameter of 1.9 mm. The volume of sample injected into the column was 1 µL. Chromatographic analysis, total duration of 8 min, was on the gradient of the following solvents: t = 0 min, methanol/water 50:50; 0 < t < 4 min, a linear increase in the proportion of methanol to a methanol/water ratio of 95:5; 4 < t < 6 min, methanol/water 95:5; 6 < t < 7 min, a linear decrease in the proportion

of methanol to return to a methanol/water ratio of 50:50; 6 < t < 7 min, methanol/water 50:50. The water used was buffered with ammonium acetate 5 mM. The flow rate of the mobile phase was 0.3 mL/min, at the Faculté de Pharmacie of Marseille.

The high-resolution mass spectrum was recorded on an SYNAPT G2 HDMS (Waters, 34 Maple St, Milford, MA, USA) equipped with a pneumatically assisted atmospheric pressure ionization (API) source. The sample was ionized in positive electrospray mode under the following conditions: electrospray voltage—2.8 kV; orifice voltage—20 V; nebulizing gas flow rate (nitrogen)—100 L/h. The sample was dissolved in 300 µL of dichloromethane and then diluted 1:103 in a solution of methanol with 3 mM ammonium acetate. The extract solution was introduced into the ionization source via in-fusion at a flow rate of 10 µL/min. The exact mass measurement was performed in triplicate with external calibration. HRMS was performed at the Faculté des Sciences de Saint-Jérôme (Marseille, France). Elemental analysis was performed on a Flash EA 1112 (Thermo Fisher Scientific, Waltham, MA, USA), controlled by Eager Xperience software (Ver. 1.2), under the conditions: temperature—970 °C, carrier gas—helium, gas flow rate—140 mL/min, detector catharometer, performed at the Faculté des Sciences de Saint-Jérôme (Marseille, France).

NMR spectra were recorded on a Bruker Avance NEO 400 MHz NanoBay spectrometer at the Faculté de Pharmacie of Marseille. Residual ^{1}H and ^{13}C peaks in deuterated solvent ($CDCl_3$) were used for chemical shift calibration without the need for an additional internal standard. ^{1}H NMR: reference $CDCl_3$ δ = 7.26 ppm and ^{13}C NMR: reference $CDCl_3$ δ = 77.16 ppm. Data for ^{1}H NMR are reported as follows: chemical shifts (δ) in parts per million (ppm), multiplicity (described as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublet; ddd, doublet of doublet of doublet; m, multiplet), coupling constants (*J*) in Hertz (Hz) and integration. Data for ^{13}C NMR are reported as follows: chemical shifts (δ) in parts per million (ppm).

*3.2. 2-Nitro-4-vinylbenzonitrile (**1**)*

A microwave vial of 20 mL was charged with 4-bromo-2-nitrobenzonitrile (500 mg, 1.0 equiv.), vinylboronic acid pinacol ester (1.2 equiv.), potassium carbonate (3.0 equiv.) and tetrakis(triphenylphosphine)palladium (0) (5 mol%). The system was capped and a mixture of 4 mL of dioxane–water (3:1) was introduced under nitrogen atmosphere. The reaction mixture was stirred at 120 °C for the appropriate time. The TLC monitoring reaction was performed using cyclohexane-AcOEt (7:3) as an eluent and visualized with ultraviolet light under a UV-Lamp VL-6.CL., 254 nm (6 W), with a retardation factor of 0.61, and verified via low-resolution LC-MS. The reaction mixture was poured into cold water and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine, dried over sodium sulphate and the solvent was removed in vacuo. Then, the obtained crude was purified via column chromatography on silica gel from 90:10 to 50:50 of petroleum ether/dichloromethane, to afford the desired product with a yield of 81% (310 mg). The product was obtained as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32 (s, 1H, CH_{Ar}), 7.86 (d, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 1H, CH_{Ar}), 7.78 (d, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 1H, CH_{Ar}), 6.80 (dd, $^{3}J_{H\text{-}H}$ = 10.9 Hz, $^{3}J_{H\text{-}H}$ = 17.6 Hz, 1H, CH), 6.05 (d, $^{3}J_{H\text{-}H}$ = 17.6 Hz, 1H, H-CH_2), 5.66 (d, $^{3}J_{H\text{-}H}$ = 10.9 Hz, 1H, H-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.6 (C), 135.9 (CH_{Ar}), 133.6 (CH_{Ar}), 131.4 (CH_{Ar}), 122.9 (CH_{Ar}), 121.1 (2C), 115.2 (C), 106.4 (C). Analysis calculated for $C_9H_6N_2O_2$: C 62.07%, H 3.47%, N 16.09%, and found C 62.07%, H 3.41%, N 15.99%. LC/MS ESI+ t_R 4.46 min, (*m*/*z*) $[M + Na]^+$ 197.29/197.15. Mp 113–114 °C.

*3.3. 4-(2-((4-Fluorophenyl)sulfonyl)acetyl)-2-nitrobenzonitrile (**2**)*

A mixture of 2-nitro-4-vinylbenzonitrile (1) (270 mg, 1.55 mmol), sulfonylhydrazide (1.55 mmol), $Cu(OAc)_2$ (5 mol%), and EtOH (6 mL) in a 25 mL round-bottomed flask was placed under O_2 (balloon). The reaction vessel was allowed to stir at 80 °C for 72 h. The TLC monitoring reaction was performed using cyclohexane-AcOEt (1:1) as an eluent and visualized with ultraviolet light under a UV-Lamp VL-6.CL., 254 nm (6 W), with a retardation factor of 0.45, and verified via low-resolution LC-MS. After the reaction, the

resulting mixture was concentrated under vacuum and the residue was purified by flash column chromatography using a mixture of petroleum ether—AcOEt (from 9:1 to 4:6) as an eluent to give the desired product as a light brown solid with a yield of 39% (196 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.88 (s, 1H, CH_{Ar}), 8.45 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, CH_{Ar}), 8.12 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, CH_{Ar}), 7.92–7.89 (m, 2H, CH_{Ar}), 7.34–7.29 (m, 2H, CH_{Ar}), 4.79 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 185.4 (C), 166.7 (d, $J_{C\text{-}F}$ = 258.9 Hz, C), 149.2 (C), 139.4 (C), 136.6 (CH_{Ar}), 134.3 (CH_{Ar}), 134.0 (C), 131.7 (d, $J_{C\text{-}F}$ = 9.8 Hz, 2CH_{Ar}), 126.0 (CH_{Ar}), 117.1 (d, $J_{C\text{-}F}$ = 23.0 Hz, 2CH_{Ar}), 114.1 (C), 112.6 (C), 64.1 (CH_2). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) −100.6. Analysis calculated for $C_{15}H_9FN_2O_5S$: C 51.73%, H 2.60%, N 8.04%, and found C 52.10%, H 2.58%, N 8.18%. LC/MS ESI+ t_R 4.39 min, (*m*/*z*) $[M + 2Na]^+$ 197.40/197.14. Mp 128–129 °C.

*3.4. 4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-2-nitrobenzonitrile (**3**)*

In a microwave vial of 20 mL equipped with a stirring bar, a solution of manganese (III) acetate dihydrate (2.1 equiv.) and copper (II) acetate (1 equiv.) in 12 mL of glacial acetic acid was heated at 80 °C under microwave irradiation for 15 min. Then, the reaction mixture was cooled and compound 2 (165 mg, 0.48 mmol, 1 equiv.) and 2-methyl-3-phenyl-1-propene (2 equiv.) in 13 mL of acetic acid were introduced. The reaction mixture was heated for 2.5 h under microwave irradiation under the same conditions. The TLC monitoring reaction was performed using cyclohexane-AcOEt (6:4) as an eluent and visualized with ultraviolet light under a UV-Lamp VL-6.CL., 254 nm and 365 nm (6 W), with a retardation factor of 0.54. The resulting product was poured into 50 mL of cold water and extracted with dichloromethane (3 × 40 mL). The organic extracts were collected and washed with saturated aqueous $NaHCO_3$ (3 × 40 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified via column chromatography (silica gel; eluent: cyclohexane-AcOEt from 9:1 to 7:3) affording the title product as a white oily solid and verified via HRMS. Yield: 37% (84 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.45 (d, $^{4}J_{H\text{-}H}$ = 1.6 Hz, 1H, CH_{Ar}), 8.06 (dd, $^{4}J_{H\text{-}H}$ = 1.6 Hz, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, CH_{Ar}), 7.94 (d, $^{3}J_{H\text{-}H}$ = 8.2 Hz, 1H, CH_{Ar}), 7.58–7.54 (m, 2H, 2CH_{Ar}), 7.24–7.12 (m, 5H, 5CH_{Ar}), 7.05 (d, $^{3}J_{H\text{-}H}$ = 8.2 Hz, 2H, 2CH_{Ar}), 3.04 (d, $^{2}J_{H\text{-}H}$ = 14.7 Hz, 2H, CH_2), 2.92–2.82 (m, 2H, CH_2), 1.43 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6 (d, $J_{C\text{-}F}$ = 255.9 Hz, C), 157.5 (C), 136.7 (d, $J_{C\text{-}F}$ = 3.5 Hz, C), 135.2 (CH_{Ar}), 135.1 (CH_{Ar}), 135.0 (2C), 134.4 (C), 130.3 (2CH_{Ar}), 129.8 (d, $J_{C\text{-}F}$ = 10.1 Hz, 2CH_{Ar}), 128.5 (2CH_{Ar}), 127.4 (CH_{Ar}), 126.4 (CH_{Ar}), 116.8 (d, $J_{C\text{-}F}$ = 22.5 Hz, 2CH_{Ar}), 114.6 (C), 113.7 (C), 109.5 (C), 89.9 (C), 46.7 (CH_2), 41.7 (CH_2), 27.7 (CH_3). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) −103.5. $C_{25}H_{19}FN_2O_5S$: HRMS: *m*/*z* $[M + Na]^+$ calculated 501.0891; found 501.0891.

*3.5. 4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-2-nitrobenzamide (**4**)*

In a microwave vial of 20 mL equipped with a stirring bar, a solution of compound 3 (45 mg, 0.09 mmol), in water (2 mL) and ethanol (9 mL) was inserted. Hydroxylamine hydrochloride (26 mg, 0.38 mmol, 4 equiv.) and sodium carbonate (20 mg, 0.19 mmol) were added. The mixture was heated at 90 °C under N_2 and microwave irradiation for 1h. The TLC monitoring reaction was performed using DCM/MeOH (4%) as an eluent and visualized with ultraviolet light under a UV-Lamp VL-6.CL., 254 nm (6 W), with a retardation factor of 0.45. The reaction was allowed to cool, and the ethanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), the combined organic fractions were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified via column chromatography (silica gel; eluent: DCM/MeOH from 2% to 4%) affording the title product as a white oily solid and verified via HRMS. Yield 85% (37 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17 (d, $^{4}J_{H\text{-}H}$ = 1.6 Hz, 1H, CH_{Ar}), 7.91 (dd, $^{4}J_{H\text{-}H}$ = 1.6 Hz, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 1H, CH_{Ar}), 7.60 (d, $^{3}J_{H\text{-}H}$ = 8.0 Hz, 1H, CH_{Ar}), 7.57–7.52 (m, 2H, 2CH_{Ar}), 7.24–7.10 (m, 5H, 5CH_{Ar}), 7.05 (d, $^{3}J_{H\text{-}H}$ = 7.7 Hz, 2H, 2CH_{Ar}), 6.09 (br s, 2H, NH_2), 3.03 (d, $^{2}J_{H\text{-}H}$ = 13.9 Hz, 1H, CH_2), 3.02 (d, $^{2}J_{H\text{-}H}$ = 14.8 Hz, 1H, CH_2), 2.88 (d, $^{2}J_{H\text{-}H}$ = 14.8 Hz, 1H, CH_2), 2.83 (d,

$^{2}J_{H\text{-}H}$ = 13.9 Hz, 1H, CH_2), 1.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8 (C), 165.6 (d, $J_{C\text{-}F}$ = 255.5 Hz, C), 159.0 (C), 145.9 (C), 137.1 (C), 135.2 (C), 134.9 (CH_{Ar}), 133.8 (C), 131.6 (C), 130.4 ($2CH_{Ar}$), 129.8 (d, $J_{C\text{-}F}$ = 9.6 Hz, $2CH_{Ar}$), 128.5 ($2CH_{Ar}$), 128.3 (CH_{Ar}), 127.3 (CH_{Ar}), 125.5 (CH_{Ar}), 116.7 (d, $J_{C\text{-}F}$ = 23.5 Hz, $2CH_{Ar}$), 112.1 (C), 89.5 (C), 46.7 (CH_2), 41.6 (CH_2), 27.7 (CH_3). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) −103.9. $C_{25}H_{21}FN_2O_6S$: HRMS: m/z $[M + NH_4]^+$ calculated 514.1443; found 514.1443.

*3.6. 4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N′-hydroxy-2-nitrobenzimidamide (**5**)*

A suspension of hydroxylamine hydrochloride (10 equiv.) in DMSO was stirred under inert atmosphere and cooled to 0 °C. Potassium *tert*-butoxide (10 equiv.) was added gradually, and the reaction mixture was stirred for 30 min. Then, compound 3 was added (30 mg, 0.08 mmol, 1 equiv.), and the reaction mixture was stirred for 18 h at room temperature. The TLC monitoring reaction was performed using DCM-MeOH (96:4) as an eluent and visualized with ultraviolet light under a UV-Lamp VL-6.CL., 254 and 365 nm (6 W), with a retardation factor of 0.39. The resulting mixture was poured into cold water. Then, the reaction mixture was extracted with EtOAc (3 × 15 mL), and the organic layers were combined, washed with water (1 × 20 mL), brine (1 × 20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified via column chromatography (eluent: dichloromethane/MeOH 98/2): yield 80% (33 mg). The product was obtained as a yellow oily solid and verified via HRMS. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (s, 1H, CH_{Ar}), 7.89 (d, $^{3}J_{H\text{-}H}$ = 8.6 Hz, 1H, CH_{Ar}), 7.66 (d, $^{3}J_{H\text{-}H}$ = 8.5 Hz, 1H, CH_{Ar}), 7.57–7.52 (m, 2H, CH_{Ar}), 7.23–7.03 (m, 7H, CH_{Ar}), 5.12 (br s, 2H, NH_2), 3.03 (d, $^{2}J_{H\text{-}H}$ = 14.5 Hz, 2H, CH_2), 2.89–2.82 (m, 2H, CH_2), 1.53 (s, 3H, CH_3). OH not observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.5 (d, $J_{C\text{-}F}$ = 255.9 Hz, C), 159.1 (C), 150.4 (C), 148.0 (C), 137.1 (C), 135.3 (C), 134.1 (CH_{Ar}), 131.7 (C), 130.9 (CH_{Ar}), 130.4 ($2CH_{Ar}$), 129.8 (d, $J_{C\text{-}F}$ = 9.7 Hz, $2CH_{Ar}$), 128.8 (C), 128.5 ($2CH_{Ar}$), 127.3 (CH_{Ar}), 125.3 (CH_{Ar}), 116.7 (d, $J_{C\text{-}F}$ = 22.8 Hz, $2CH_{Ar}$), 112.2 (C), 89.5 (C), 46.7 (CH_2), 41.7 (CH_2), 27.6 (CH_3). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ (ppm) −104.1. $C_{25}H_{22}FN_3O_6S$: LC/MS ESI+ t_R 8.10 min, *(m/z)* $[M + H]^+$ 511.8/511.52; HRMS: m/z $[M + Na]^+$ calculated 534.1106; found 534.1105.

4. Conclusions

This study highlights the formation of the product 4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-2-nitrobenzamide, formed through a method conventionally yielding to the amidoxime in major yields. Two complementary effects have been theorized to explain this unexpected result. First an electronic effect associated with the presence of the nitro moiety and a solvation by the protic solvent. Considering that the formation of the amide derivative is mainly linked to the O-attack of hydroxylamine it was hypothesized that the electron effect could favor a more stable transition state prior to the amide formation. These conditions are not present when DMSO is used then the desired product 4-(5-Benzyl-3-((4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-*N*′-hydroxy-2-nitrobenzimidamide can be obtained. This original compound, featuring a nitro group in the ortho position to the amidoxime moiety, will be further evaluated, both in the field of medicinal chemistry and in other relevant areas.

Supplementary Materials: The following are available online: Figure S1: LC-MS spectra of compound **1**, Figure S2: LC-MS spectra of compound **2**, Figure S3: HRMS spectra of compound **3**, Figure S4: HRMS spectra of compound **4**, Figure S5: HRMS spectra of compound **5**, Figures S6–S15: ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **4** and **5**.

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