Communication

1-(Pyrrolidin-1-yl)naphtho[1,2-*d*]isoxazole

Ioannis E. Gerontitis , Abdul kadar Shaikh , Dimitrios Alivertis , Petros G. Tsoungas , George Varvounis *

Posted Date: 16 February 2025

doi: 10.20944/preprints202502.1105.v1

Keywords: heterocycle; naphtho[1,2-*d*]isoxazole; naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]-oxazinone; *o*-naphthoquinone nitrosomethide

 doi:10.20944/preprints202502.1105.v1

Communication

1-(Pyrrolidin-1-yl)naphtho[1,2-*d*]isoxazole

Ioannis E. Gerontitis [1], Abdul kadar Shaikh [1], Dimitrios Alivertis [2], Petros G. Tsoungas [3] and George Varvounis [1,*]

[1] Section of Organic Chemistry and Biochemistry, Department of Chemistry, University of Ioannina, 451 10 Ioannina, Greece

[2] Department of Biological Applications and Technology, University of Ioannina, 451 10 Ioannina, Greece

[3] Department of Biochemistry, Hellenic Pasteur Institute, 127 Vas. Sofias Ave., 115 21 Athens Greece

* Correspondence: gvarvoun@uoi.gr

Abstract: In this study, we examined the oxidation of (*E*)-2-hydroxy-1-naphthaldehyde oxime with lead tetraacetate in tetrahydrofuran that produced novel (*E*)-7a,8,9,10-tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-one oxime and 1-(pyrrolidin-1-yl)naphtho[1,2-*d*]isoxazole, and, known 7a,8,9,10-tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo-[2,1-*b*][1,3]oxazin-12-one, in 15, 18 and 10% yields, respectively. The oxime is readily hydrolysed to its corresponding ketone. Modifying the oxidants and reaction conditions did not improve the product yields. Based on previous studies in our laboratory, we proposed that the reactions proceed via the formation of an *o*-naphthoquinone nitrosomethide intermediate. ^{1}H and ^{13}C NMR, HRMS, IR, and UV-VIS spectra provided information that supported the structure of the products.

Keywords: heterocycle; naphtho[1,2-*d*]isoxazole; naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]-oxazinone; *o*-naphthoquinone nitrosomethide

1. Introduction

Benzo[*d*]isoxazole (or 1,2-benzisoxazole) is one of the most significant scaffolds in medicinal chemistry today. 3-Substituted benzo[*d*]isoxazoles display a broad range of bioactivities, including antimicrobial, anticonvulsant, antitubercular, antipsychotic, anticancer, antithrombotic and, acetylcholinesterase inhibition properties [1]. The importance of these compounds is further highlighted by United States FDA-approved drugs such as Zonisamide [2], an antiepileptic, and the antipsychotics, Risperidone [3] and Paliperidone [4]. The synthesis of benzo[*d*]isoxazoles has been adequately covered in the literature [5–7].

Naphtho[1,2-*d*]isoxazoles have been studied much less. The first derivative to be reported was the parent compound which was synthesized by the cyclodehydration of 2-hydroxy-1-naphthaldehyde oxime with acetic anhydride [8]. 2-Hydroxy-1-naphthaldehyde oxime was also cyclodehydrated to naphtho[1,2-*d*]isoxazole with TsCl and Et_3N [9]. During the synthesis of diazonaphthoquinones from the corresponding naphthols by diazo transfer from 2-azido-1,3-dimethylimidazolinium chloride, the use of

 doi:10.20944/preprints202502.1105.v1

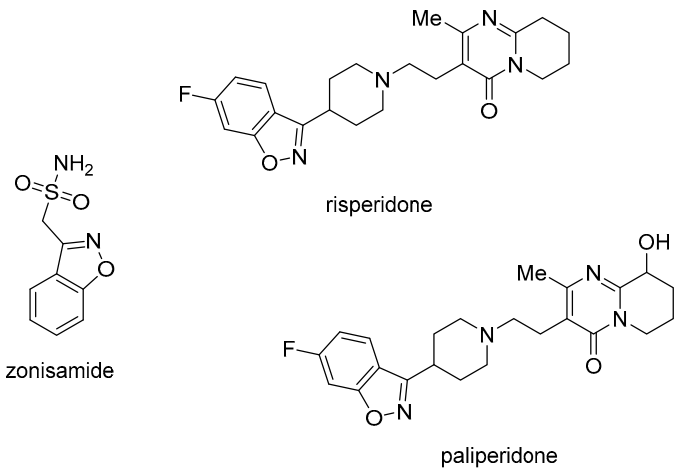


Figure 1. FDA-approved 3-substituted benzo[*d*]isoxazole drugs.

2-hydroxy-1-naphthaldehyde afforded naphtho[1,2-*d*]isoxazole and 1-diazo-2(1*H*)naphthalenone in 70 and 10% yields, respectively [10,11]. The azido complex derived from 2-hydroxy-1-naphthaldehyde and $TMSN_3$ in the presence of $ZrCl_4$, underwent nitrogen extrusion reactions to produce naphtho[1,2-*d*]isoxazole and 2-hydroxy-1-naphthonitrile in 65 and 15% yields, respectively [12]. The synthesis of 1-substituted naphtho[1,2-*d*]-isoxazoles is limited to 1-aryl, phenyl or hydroxy substituents. 1-(Aryl or phenyl)naphtho[1,2-*d*]isoxazoles were prepared by the oxidative cyclisation of 1-[(2-hydroxynaphthalen-1-yl)(aryl or phenyl)methyl]ureas with $PhI(OAc)_2$ [13]. Transformation of 2-hydroxy-1-naphthonitrile and 1-bromo-4-methoxybenzene into 1-(4-methoxyphenyl)naphtho[1,2-*d*]isoxazole was achieved by a Barbier–Grignard–type reaction mediated by PPh_3–Mg [14]. A PPh_3–DIAD–triggered Mitsunobu heterocyclization of *N*,2-dihydroxy-1-naphthamide and diisopropyl azodicarboxylate led to naphtho[1,2-*d*]isoxazol-1-ol [15].

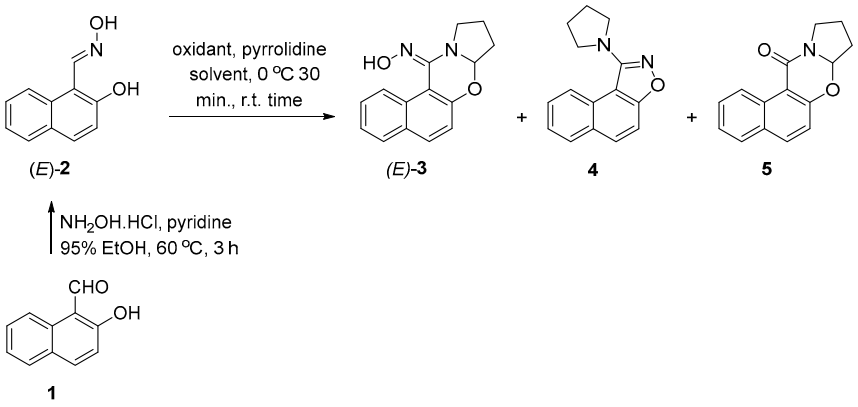
The first synthesis of parent 7a,8,9,10-tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-one was accomplished by coupling of phenyl 2-hydroxy-1-naphthoate to 3-(1,3-dioxolan-2-yl)propan-1-amine under microwave irradiation and deacetalization–bicyclization of intermediate amide using $SnCl_2{\cdot}2H_2O$ [16]Six years later the same parent compound was synthesized by a copper catalyzed intramolecular dehydrogenative (sp^3)C–O bond formation in *N*,*N*-dibenzyl-2-hydroxy-3,5-dinitrobenzamide [17].

2. Results

As illustrated in **Scheme 1** and **Table 1**, (*E*)-2-hydroxy-1-naphthaldehyde oxime (**2**) [18] was prepared, in 96% yield, by heating commercially available 2-hydroxy-1-naphthaldehyde (**1**) with five equivalents of hydroxylamine hydrochloride in 95% ethanol, along with pyridine, at 60 °C for 3 h. Following workup with ethyl acetate and 1 M HCl, the product was obtained without the need for further purification. The oxidation of (*E*)-**2** occurred with 2 equivalents of lead(IV) acetate (LTA) in the presence of 1.5 equivalents of pyrrolidine in anhydrous THF at 0 °C for 30 minutes and then at room temperature for 12 h. TLC examination of the dark reaction mixture revealed the consumption of starting material (*E*)-**2** and the appearance of 3 new main spots, together with several faint spots and a polar spot. The workup consisted of adding a 5% sodium bicarbonate solution, followed by extraction with DCM, drying of the solvent, and evaporation, which left a dark oily residue. This residue was subjected to flash column chromatography, yielding (*E*)-7a,8,9,10-tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo-[2,1-*b*][1,3]oxazin-12-one oxime (**3**), 1-(pyrrolidin-1-yl)naphtho[1,2-*d*]isoxazole (**4**) and 7a,8,9,10-tetrahydro-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-one (**5**) [16,17] in 15, 18 and 10% yield, respectively. This experiment, the workup and purification of products was used for all further experiments (**Table 1**) with appropriate changes of oxidant, equivalents of pyrrolidine, solvent and time. Thus, to assess the effectiveness of the related reagents, phenyliodine(III) diacetate [$PhI(OAc)_2$, PIDA], phenyliodine(III) bis(trifluoroacetate) [$PhI(OCOCF_3)_2$, PIFA], and μ-oxobis[phenyl-

 doi:10.20944/preprints202502.1105.v1

(trifluoromethoxy)iodine(III)] {[(PhI(OCOCF$_3$)]$_2$O, μ-oxo-bridged PIFA}, the experiment was conducted three times, each time substituting LTA with one of these reagents. Because μ-oxo-bridged PIFA was insoluble in THF, DCM was used instead (**Table 1**, entry 6. The results showed that the yields of (*E*)-**3**, **4** and **5** after the oxidation of (*E*)-**2** with PIDA in THF, were lower than the corresponding yields of (*E*)-**2** with LTA in THF. (*E*)-**2** with PIFA in THF produced even lower yields of (*E*)-**3**, **4** and **5**. The oxidation of (*E*)-**2** with μ-oxo-bridged PIFA in DCM resulted in 6 faint spots and polar material that moved on TLC as a streak when eluted with methanol. It was thus concluded that attempting to separate the components of this reaction by flash column chromatography or HPLC would not be of any synthetic value. The oxidation of (*E*)-**2** with PIDA or PIFA in DCM followed



Scheme 1. Synthesis of oxime (*E*)-**2** and its oxidation using LTA, PIDA, PIFA or μ-oxo-bridged PIFA in THF, DCM or MeCN with pyrrolidine as nucleophile for 8 or 12 h (**Table 1**.).

Table 1. Screening of Oxidants and Reaction Conditions [1].

entry	oxidant (equiv.)	pyrrolidine (equiv.)	solvent	time (h)	(*E*)-3 (yield%)[2]	4 (yield%)[2]	5 (yield%)[2]
1	LTA (2)	(1.5)	THF	12	15	18	10
2	PIDA (2)	(1.5)	THF	12	9	12	8
3	PIFA (2)	(1.5)	THF	12	6	8	7
4	PIDA (2)	(1.5)	DCM	12	10	14	7
5	PIFA (2)	(1.5)	DCM	12	6	9	4
6	μ-oxo-bridged PIFA (1)	(1.5)	DCM	12	–	–	–
7	PIDA (2)	(1.5)	MeCN	12	13	16	9
8	PIDA (3)	(2.5)	THF	8	7	14	10
9	PIDA (3)	(2.5)	DCM	8	8	15	11
10	PIDA (3)	(2.5)	MeCN	8	9	13	12

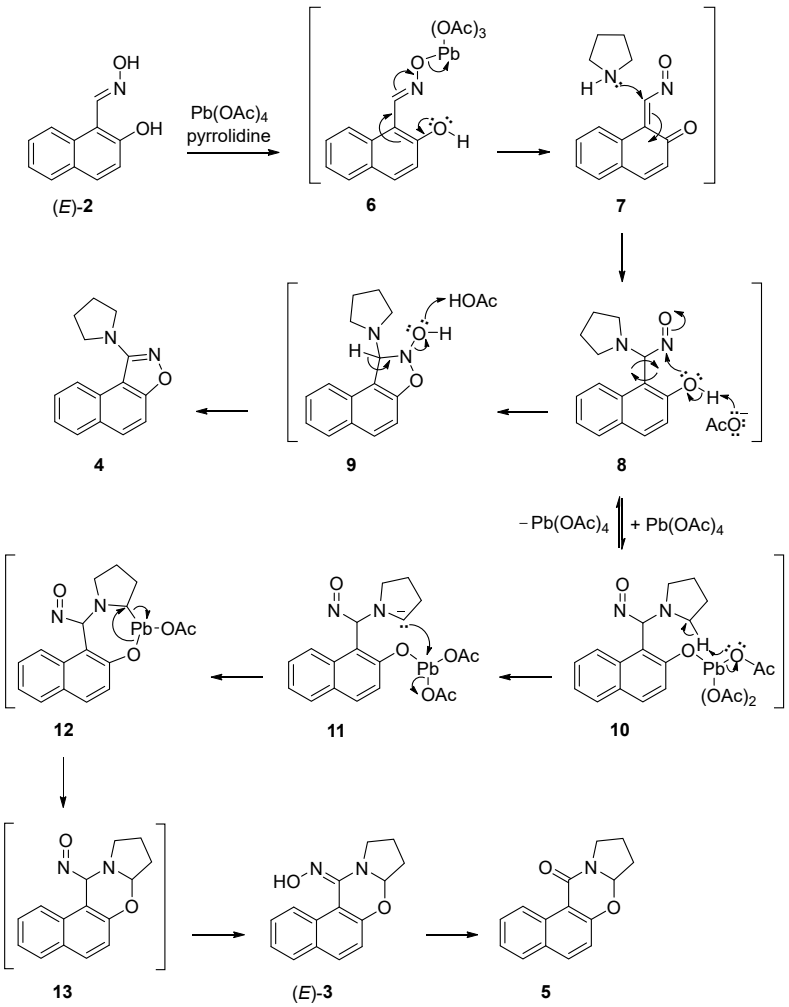
[1]Reactions were carried out by dissolving (*E*)-**2** (1 equiv.) in THF, DCM, or MeCN under a N_2 atmosphere, cooling the mixture to 0 °C, adding pyrrolidine (1.5 or 2.5 equiv.), and then gradually introducing the appropriate oxidant (1, 2 or 3 equiv.). The mixture was stirred for 30 min. at 0 °C, followed by continuous stirring at r.t. for 8 or 12 h. [2]Isolated yield.

the same trend and produced lower yields of (*E*)-**3**, **4** and **5** than the corresponding yields of (*E*)-**2** with LTA in THF. Again, the yields of (*E*)-**3**, **4** and **5** from (*E*)-**2** and PIFA in DCM are again lower than the respective yields from (*E*)-**2** and PIDA in DCM (**Table 1**, entries 4 and 5). Better yields, but slighly lower than the first reaction (**Table 1**, entry 1), were obtained from (*E*)-**2** and PIDA in MeCN (**Table 1**, entry 7). Since PIDA showed to be the next promising oxidant after LTA, the next three oxidations used 3.0 equivalents of PIDA and 2.5 equivalents of pyrrolidine, in THF, DCM or MeCN (**Table 1**, entries 8, 9 and 10). The starting material (*E*)-**2** in these reactions was consumed in 8 hours

 doi:10.20944/preprints202502.1105.v1

and 3 main spots, together with several faint spots and a polar spot, appeared after TLC examination while workup and the separation of products by flash column chromatography, was similar to the first reaction (**Table 1**, entry 1). The yields of (*E*)-**3**, **4** and **5** from the oxidation of (*E*)-**2** with PIDA, in THF, DCM or MeCN, were again lower than the corresponding yields from the oxidation of (*E*)-**2** by LTA in THF (**Table 1**, entry 1). Therefore, increasing the equivalents of PIDA and pyrrolidine, as well as conducting the oxidations in three different solvents, did not affect the outcome of the reaction or substantially alter the yields of the three products.

For the formation of products (*E*)-**3**, **4** and **5** we propose (**Scheme 2**) that the oxygen atom of the aldoxime group of (*E*)-**2**, displaces acetate anion from LTA to form the organolead intermediate **6**, having eliminated acetic acid. From complex **6** lead(II) acetate and acetic acid are eliminated to furnish *o*-naphthoquinone nitrosomethide **7**, which then undergoes Michael addition by pyrrolidine onto the N=O bearing exocyclic alkene carbon atom, to afford nitroso adduct **8**. Cyclisation of **8** by a 5-exo-trig addition reaction between hydroxy and nitroso groups forms the intermediate 1-pyrrolidin-1-ylnaphtho[1,2-*d*]isoxazol-2(1*H*)-ol **9**. On the other hand, a free rotation about the benzylic σ-bond of **8** and reaction of the naphthol OH with LTA leads to organolead intermediate **10**. Intramolecular abstraction of the acidic proton of the pyrrolidine group in **10** and elimination of acetic acid, gives intermediate carbanion **11**, which cyclises to intermediate naphthopyrrolo-oxazaplumbepine **12**, by eliminating acetate ion. Rearrangement of the lead and oxygen atoms in compound **12** affords 12-nitrosonaphthopyrrolooxazine **13** which in the presence of acid tautomerizes to the oxime (*E*)-**3**. The oxime is unstable in the presence of LTA and is hydrolized to the ketone **5**.



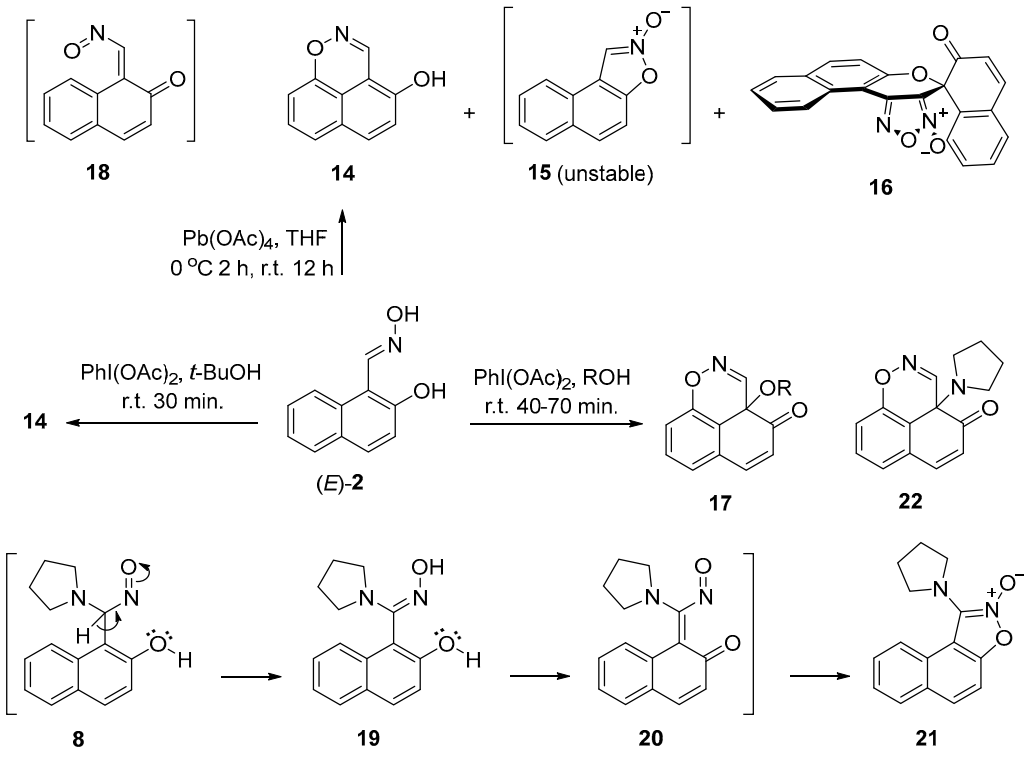
Scheme 2. Proposed mechanism for oxidative generation of *o*-naphthoquinone nitrosomethide **7** from (*E*)-2-hydroxy-1-naphthaldehyde oxime (**2**), Michael addition and further reactions.

 doi:10.20944/preprints202502.1105.v1

3. Discussion

In our earlier work, the oxidative cyclisation of (*E*)-**2** with LTA in THF, lead to the formation of 4-hydroxynaphtho[1,8-*de*][1,2]oxazine **14** and naphtho[1,2-*d*]isoxazole 2-oxide **15**. [19]. The latter compound was isolated only once by chance. Thereafter, whenever the reaction was repeated, **14** and spiro dimer **16** were isolated (**Scheme 3**) [20]. Oxidative *peri*-cyclization and alkoxylation of (*E*)-**2** to 3a-alkoxynaphtho[1,8-*de*][1,2]oxazin-4(3*aH*)-ones **17** was achieved using $PhI(OAc)_2$ in various aliphatic alcohols. When the alcohol in this reaction was the non-nucleophilic *t*-BuOH, only oxidative *peri*-cyclization occurred to give **14**. [21]. These reactions have been rationalized by invoking the agency of the *peri*-orientated *o*-naphthoquinone nitrosomethide **18** generated from the oxidation of oxime (*E*)-**2**. The intriguing structural features reflected on the reactivity profile of this intermediate have been reported [22,23].

At the start of the present work, we repeated the oxidation of (*E*)-**2** with LTA in THF (**Scheme 3**) but this time adding pyrrolidine as nucleophile (**Table 1**, entry 1). We anticipated that the *in situ* generated *o*-naphthoquinone nitrosomethide **7** (**Scheme 2**) would function as Michael acceptor towards pyrrolidine and form nitroso intermediate **8** (**Scheme 2**). The latter is expected to tautomerize to oxime **19**, oxidize to *o*-naphthoquinone nitrosomethide **20** and then undergo 6π-electrocyclization to **21**. In the literature there are many examples of 3-substituted benzo[*d*]isoxazole 2-oxides [24,25]. The same reaction is also expected to produce **14** and **16** (**Scheme 3**), depending on the efficiency of the competing Michael addition. The use of PIDA instead of LTA in the oxidation of (*E*)-**2** with pyrrolidine (**Table 1**, entries 2, 4, 7–10), was anticipated to furnish naphthooxazinone **22**, based on the reaction that gave **17**. Compounds **14**, **16**, **21** and **22** were absent in all the reactions listed in **Table 1**.



Scheme 3. Earlier work on the reactions of (*E*)-2-hydroxy-1-naphthaldehyde oxime (**2**) with $Pb(OAc)_4$ and $PhI(OAc)_2$. Analogously, products **21** and **22** could be expected for reaction of (*E*)-**2**.

Products (*E*)-**3**, **4** and **5** were characterized using UV–VIS, IR, ^1H and ^{13}C NMR spectroscopy and, HRMS spectrometry (see Supplementary Materials for the mentioned spectra) that confirmed their molecular formulae. The UV–VIS spectrum of (*E*)-**3** showed two strong absorptions at 284.6 nm and 339.2 nm, which fall within the absorption range typically observed for unsubstituted naphthalene. In the IR spectrum, the (OH) str. absorption band is not visible in the region 3400–3300 cm^{-1} probably

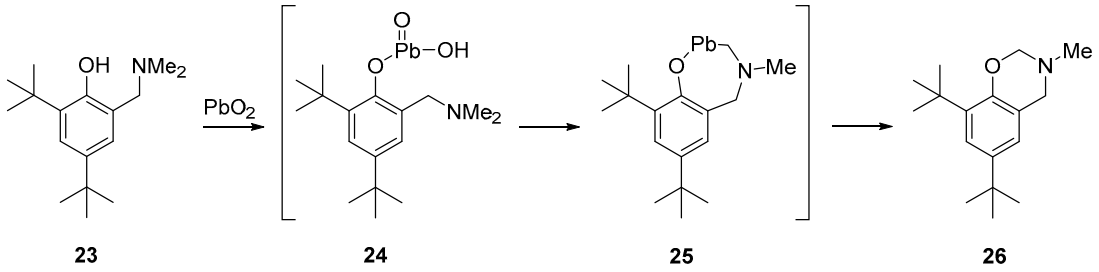
 doi:10.20944/preprints202502.1105.v1

due to hydrogen bonding, the absorption band at 3063 (w) cm^{-1} was assigned to aromatic C-H str. and at 2910 (w) to aliphatic C-H str. while the absorption bands at 1618 (m) and 1588 (m) cm^{-1} were assigned to aromatic C=C str. vibrations. In the ^{1}H NMR spectrum of product (*E*)-**3** in $CDCl_3$, the broad singlet at 10.05 ppm represented the proton of the hydroxyl group. In the aromatic region in the range of 8.66–7.25 ppm there are six aromatic protons and at 6.00 ppm the singlet was assigned to the aliphatic proton of the pyrrolidine ring. The remaining three multiplets in the pyrrolidine ring, at 3.20–2.90, 2.38–2.17, and 1.94–1.66 ppm, each integrated for two protons and were assigned to the three methylene groups. The ^{13}C NMR spectrum in $CDCl_3$ showed 15 signals as expected. High-resolution mass spectrometry analysis by ESI confirmed the expected molecular ion at *m*/*z* = 255.1125 $[M + H]^+$, which was calculated for $C_{15}H_{15}N_2O_2^+$ *m*/*z* = 255.1128. The ^{1}H and ^{13}C NMR spectroscopic data of compound **5** are in good agreement with the corresponding published data [17]. In the ^{1}H NMR spectrum of **5** in $CDCl_3$, the region from 9.15 ppm to 7.14 ppm, showed a total of 6 aromatic protons. The singlet at 5.56 ppm corresponded to the aliphatic proton of the pyrrolidine ring, while the peaks at 4.03 and 3.67 ppm, 2.49 and 2.42–2.34 ppm, and 2.18 and 2.03 ppm each integrated for one proton, with the pairs of peaks assigned to the three methylene groups in the pyrrolidine ring. The ^{13}C NMR spectrum in $CDCl_3$ showed 15 signals that agreed with the number of carbon atoms in the molecule. Furthermore, high-resolution mass spectrometry analysis that was recorded by ESI confirmed the expected molecular ion at *m*/*z* = 240.1017 $[M + H]^+$, which was calculated for $C_{15}H_{14}NO_2^+$ *m*/*z* = 240.1019. The ^{1}H NMR peaks in compound (*E*)-**3** were in a similar ppm range to those in compound **5**. Additionally, the peak at 161.45 ppm in the ^{13}C NMR spectrum of **5**, which was assigned to the carbonyl group, was not observed in the ^{13}C NMR spectrum of (*E*)-**3**. These observations provide additional support for the proposed structure of (*E*)-**3**. The UV–VIS spectrum of compound **4** showed three strong absorptions at 214.4, 233.0 and 249.6 nm. The first two are within the range of the absorptions found in unsubstituted naphthalene [26] and the third is within the range of the absorptions found in substituted isoxazoles [27]. In the IR spectrum, the absorption band at 3056 (w) cm^{-1} was assigned to aromatic C–H str., and at 2974 (w) and 2874 (w) cm^{-1} to aliphatic C–H str. while the absorption bands at 1647 (m) and 1618 (m) cm^{-1} were assigned to aromatic C=C str. vibrations. In the ^{1}H NMR spectrum of product **4** in $CDCl_3$, the doublets at 8.39 and 7.90 ppm each integrated for one proton, the multiplet in the range 7.59 ppm to 7.48 ppm integrated for three protons and the triplet at 7.45 ppm integrated for one proton. Thus, the total number of aromatic protons was six. The aliphatic signals in the region 3.82 ppm and 3.71 ppm integrate for four protons and together with the signals in the region 2.15 ppm to 2.04 ppm that also integrate for four protons, together represented the eight protons of the *N*-substituted pyrrolidine ring. The ^{13}C NMR spectrum showed 13 signals. Signals at 47.60 ppm and 25.66 ppm contained two equivalent carbon atoms, each bringing the total number of carbon atoms to 15, as expected. In the ^{1}H NMR spectrum of parent naphtho[1,2-*d*]-isoxazole in $CDCl_3$, there was a singlet at 9.11 ppm that corresponded to the imine proton [9]. This proton was absent in the ^{1}H NMR spectrum of product **4**. This observation excluded compound **22** from being a product since in the related compounds **17** the imine proton appears as a singlet in the region 8.33 ppm to 8.15 ppm. High-resolution mass spectrometry analysis, using ESI, confirmed the expected molecular ion of **4** at *m*/*z* = 239.1173 $[M + H]^+$, which was calculated for $C_{15}H_{15}N_2O^+$ *m*/*z* = 239.1178. The calculated *m*/*z* = 255.1134 for $C_{15}H_{15}N_2O_2^+$ $[M + H]^+$ of **21** did not appear in the HRMS spectrum of **4**.

Scheme 2 describes the proposed mechanism of the oxidation of (*E*)-**2** to **4**, (*E*)-**3** and **5**, where an analogy to the intermediacy of cyclic organolead intermediate **12** has been reported by Belostotskaya and co-workers [28] who oxidatively cyclized *o*-(dimethylaminomethyl)phenol **23** into 1,3-benzoxazine **26** (**Scheme 4**), via the proposed cyclic organolead intermediate **25**.

In the last step of the mechanism outlined in **Scheme 2**, it was proposed that oxime (*E*)-**3** undergoes hydrolysis to form the ketone **5**. The reaction of ketoximes with Koser's reagent [PhI(OH)OTs] in tetrahydrofuran was reported [29] to afford the corresponding ketones, supporting this hypothesis.

 doi:10.20944/preprints202502.1105.v1



Scheme 4. Proposed mechanism by Belostotskaya and co-workers for the oxidation of **23** to 1,3-benzoxazine **26** via the cyclic organolead intermediate **25**.

Our expectation from the present research was that the main product of this reaction would be 1-(pyrrolidin-1-yl)naphtho[1,2-*d*]isoxazole (**4**), and we had hoped that this would provide a method to introduce nucleophiles in position 1 of naphtho[1,2-*d*]isoxazole. While there was initial interest in synthesizing a series of 3-substituted naphtho[1,2-*d*]isoxazole derivatives to explore their biological activities, the low yield of compound **4** and the consistent formation of products (*E*)-**3** and **5** in all reaction trials, ultimately reduced enthusiasm for the project.

4. Materials and Methods

All reactions were carried out under a N_2 atmosphere. Solvents and reagents were used as received from the manufacturers (Aldrich, Acros and Alfa Aesar) except for DCM, EtOAc and hexane that were purified and dried according to recommended procedures. Organic solutions were concentrated by rotary evaporation at 23–40 °C under reduced pressure (15 Torr). Melting points were taken on a Büchi 510 apparatus (Büchi Labortechnik AG, Switzerland). The IR spectra were acquired on an Agilent Cary 630 FTIR spectrophotometer (Agilent Technologies) as a solid and reported in wave numbers (cm^{-1}). The UV spectrum was recorded using a Jasco V-630 UV-Vis spectrophotometer (Jasco Europe s.r.l., Cremella, Italy). The samples were measured in a 1 cm quartz cell at room temperature in MeCN with concentrations of 9×10^{-2}mM and 9×10^{-5}mM for (*E*)-**3**, 25×10^{-6}mM for **4** and, 1×10^{-1}mM and 1×10^{-2}mM for **5**. Samples for ^{1}H and ^{13}C NMR experiments were dissolved in dry DMSO-d_6 or $CDCl_3$ and were recorded on a Brüker Avance 400 MHz spectrometer (Brüker BioSpin GmbH, Rheinstetten, Germany). The chemical shifts (δ) were reported in ppm and referenced to residual solvent signals. Coupling constants (*J*) were given in Hz. The high-resolution ESI mass spectrum was measured on a ThermoFisher Scientific Orbitrap XL system (Thermo Fisher Scientific, Waltham, MA, USA). Analytical thin layer chromatography (TLC) was performed with Merck 70–230-mesh silica gel precoated TLC aluminium plates. TLC plates were observed under UV light at 254 and 365 nm. Preparative flash chromatography was carried out using Merck 9385 silica gel.

4.1. (E)-7a,8,9,10-Tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazin-12-one oxime (3), 1-(pyrrolidin-1-yl)naphtho[1,2-d]isoxazole (4) and 7a,8,9,10-Tetrahydro-12H-naphtho[1,2-e]pyrrolo-[2,1-b][1,3]oxazin-12-one (5)

To a stirred solution of *(E)*-2-hydroxy-1-naphthaldehyde oxime **2** (200 mg, 1.068 mmol, 1 equiv) in dry THF (10 mL) at 0 °C, under a nitrogen atmosphere, pyrrolidine (113 mg, 1,6 mmol, 1.5 equiv) was added followed by a slow addition of $Pb(OAc)_4$ (940 mg, 2.136 mmol, 2 equiv). The reaction was stirred at 0 °C for 30 min and then at room temperature for 12 h. TLC examination revealed the absence of the starting material spot and the presence of three new spots (visualized under a UV lamp). A 5% solution of $NaHCO_3$ (20 mL) was added dropwise to bring the pH = 7–8. The THF/H_2O reaction mixture was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The acquired brown oil was purified by flash column chromatography (10% EtOAc in hexane) to give

 doi:10.20944/preprints202502.1105.v1

(*E*)-**3** (42 mg, 15% yield) as a brown solid, mp: 91–93 °C, **4** (43 mg, 18% yield) as a yellow solid, mp: 65–67 °C and **5** (26 mg, 10% yield) as a light brown oil.

4.1.1. (E)-7a,8,9,10-Tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazin-12-one oxime (3)

R_f = 0.35 (EtOAc/hexane, 20:80); UV-VIS (MeCN), nm (9 × 10^{-2}mM): λ_{max} 284.6 (log ε 12264), 339.2 (log ε 6318), nm (9 × 10^{-5}mM): λ_{max} 274.2 nm (log ε = 1604444); FTIR (solid) cm^{-1}: 3063 (w), 2910 (m), 1618 (m), 1588 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 8.66 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 6.00 (s, 1H), 3.20–2.90 (m, 2H), 2.38–2.17 (m, 2H), 1.94–1.66 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 157.30, 133.37, 131.73, 128.80, 128.64, 127.60, 124.54, 123.66, 118.59, 102.36, 98.41, 52.62, 33.58, 29.72, 23.24; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd. for $C_{15}H_{15}N_2O_2^+$: 255.1128. Found: 255.1125.

4.1.2. 1-(Pyrrolidin-1-yl)naphtho[1,2-d]isoxazole (4).

R_f = 0.2 (EtOAc/hexane, 20:80); UV-VIS (MeCN), nm (25 × 10^{-6}mM): λ_{max} 214.4 (log ε = 29368), 233.0 (log ε = 21404), 249.6 (log ε = 22156), 289.4 (log ε = 4246), 310.6 (log ε = 4936), 338.8 (log ε = 7152); FTIR (solid) cm^{-1}: 3056 (w), 2974 (w), 2874 (w), 1647 (m), 1618 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.59–7.48 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.82–3.71 (m, 4H), 2.15–2.04 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 161.19, 144.99, 138.62, 131.09, 128.33, 125.50, 124.89, 124.42, 122.33, 120.25, 109.69, 47.60 (2C), 25.66 (2C). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd. for $C_{15}H_{15}N_2O^+$: 239.1178. Found: 239.1173.

4.1.3. 7a,8,9,10-Tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazin-12-one (5).

R_f = 0.1 (EtOAc/hexane, 20:80); UV-VIS (MeCN), nm (1 × 10^{-1}mM): λ_{max} 276.2 (log ε = 3201), 289.2 (log ε = 3628), 300.6 (log ε = 4110), 341.4 (log ε = 3399), 356.6 (log ε = 2474), 390.8 (log ε = 639), 409.8 (log ε = 521), nm (1 × 10^{-2}mM): λ_{max} 212.0 (log ε = 55450), 224.2 (log ε = 56120), 251.2 (log ε = 38180), FTIR (solid) cm^{-1}: 3063 (w), 2910 (m), 1618 (m), 1588 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.67–7.59 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 5.56 (dd, *J* = 6.0, 4.4 Hz, 1H), 4.03 (dt, *J* = 13.2, 6.8 Hz, 1H), 3.67 (dt, *J* = 12.3, 6.8 Hz, 1H), 2.49 (dt, *J* = 13.3, 6.7 Hz, 1H), 2.42–2.34 (m, 1H), 2.18 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.03 (td, *J* = 13.1, 6.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 161.45, 157.69, 134.86, 131.79, 130.09, 128.35, 128.25, 126.08, 124.84, 116.96, 88.12, 45.07, 32.15, 29.70, 22.00 (spectroscopic data are in agreement with those reported in the literature [17]. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd. for $C_{15}H_{14}NO_2^+$: 240.1019. Found: 240.1017.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1: ^{1}H NMR spectrum of compound (*E*)-**3**; Figure S2: ^{13}C NMR spectrum of compound (*E*)-**3**; Figure S3: HRMS (ESI) spectrum of compound (*E*)-**3**; Figure S4: IR spectrum of compound (*E*)-**3**; Figure S5: UV spectrum of compound (*E*)-**3**; Figure S6: ^{1}H NMR spectrum of compound **4**; Figure S7: ^{13}C NMR spectrum of compound **4**; Figure S8: HRMS (ESI) spectrum of compound **4**; Figure S9: IR spectrum of compound **4**; Figure S10: UV spectrum of compound **4**; Figure S11: ^{1}H NMR spectrum of compound **5**; Figure S12: ^{13}C NMR spectrum of compound **5** Figure S13: HRMS (ESI) spectrum of compound **5**; Figure S14: IR spectrum of compound **5**; Figure S15: UV spectra of compound **5**.

Author Contributions: Conceptualization, G.V. and P.G.T.; methodology, I.E.G; investigation, A.K.S., I.E.G and D.A.; writing—original draft preparation, G.V.; writing—review and editing, G.V. and P.G.T.; supervision, G.V.; project administration, G.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Sample Availability: Samples of the compounds **2**, **3**, **4** are available from the authors.

 doi:10.20944/preprints202502.1105.v1

Acknowledgments: We appreciate the use of NMR and mass spectrometry facilities funded by the Network of Research Supporting Laboratories of the University of Ioannina and thank Dr. Vasiliki Boti for providing high-resolution mass spectra.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

LTA	Lead tetraacetate
PIDA	Phenyliodine(III) diacetate
PIFA	Phenyliodine(III) bis(trifluoroacetate)
μ-Oxo-bridged PIFA	μ-Oxo-bis[phenyl(trifluoromethoxy)iodine(III)]

References

1. Rakesh, K.P.; Shantharam, C.S.; Sridhara, M.B.; Manukumar, H.M.; Qin, H.L. Benzisoxazole: A Privileged Scaffold for Medicinal Chemistry. *Med. Chem. Comm.* 2017, *8*, 2023–2039, doi.org/10.1039/C7MD00449D.
2. Schulze-Bonhage, A. Zonisamide in the Treatment of Epilepsy Schulze-Bonhage Zonisamide. *Expert. Opin. Pharmacother.* 2010, *11*, 115–126, doi:10.1517/14656560903468728.
3. Harrison, T.C.; Goa, K.L.; Beauclair, L. *Long-Acting Risperidone. A Review of Its Use in Schizophrenia*. *CNS Drugs* **2004**, *18*, 113–132, doi:10.2165/00023210-200418020-00005.
4. Solanki, P. V.; Uppelli, S.B.; Pandit, B.S.; Mathad, V.T. An Improved and Efficient Process for the Production of Highly Pure Paliperidone, a Psychotropic Agent, via DBU Catalyzed N-Alkylation. *ACS Sustain. Chem. Eng.* **2013**, *1*, 243–248, doi:10.1021/sc3000916.
5. Lukoyanov, A.A.; Aksenova, S.A.; Tabolin, A.A.; Sukhorukov, A.Yu. 3-Halo-5,6-Dihydro-4 *H*-1,2-Oxazine *N* -Oxides as Synthetic Equivalents of Unsaturated Nitrile Oxides in the [3 + 2]-Cycloaddition with Arynes: Synthesis of Substituted 3-Vinyl-1,2-Benzisoxazoles. *Org. Biomol. Chem.* **2024**, *22*, 3615–3621, doi:10.1039/D4OB00391H.
6. Shastri, R. Review on Synthesis of 3-Substituted 1,2-Benzisoxazole Derivatives. *Chem. Sci. Trans* **2016**, doi:10.7598/cst2016.1120.
7. Giomi, D.; Cordero, F.M.; Machetti, F. Isoxazoles. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., Taylor, R.J.K., Eds.; Elsevier Science: Oxford, UK, 2008; Volume 4, pp. 365–485.
8. Mahadevan, K.M.; Vaidya, V.P.; Vagdevi, H.M. Synthesis of Novel Naphtho[2,1-*b*]Furopyrimidine Derivatives. *Indian. J. Chem. Sect. B* **2003**, *42*, 1931–1936, doi:10.1002/chin.200347155.
9. Dale, T.J.; Sather, A.C.; Rebek, J. Synthesis of Novel Aryl-1,2-Oxazoles from Ortho-Hydroxyaryloximes. *Tetrahedron Lett.* **2009**, *50*, 6173–6175, doi:10.1016/j.tetlet.2009.08.086.
10. Kitamura, M.; Sakata, R.; Tashiro, N.; Ikegami, A.; Okauchi, T. Synthesis of Diazonaphthoquinones from Naphthols by Diazo-Transfer Reaction. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 824–833, doi:10.1246/bcsj.20150021.
11. Kitamura, M.; Tashiro, N.; Sakata, R.; Okauchi, T. Synthesis of Diazonaphthoquinones from Naphthols by Diazo-Transfer Reaction with 2-Azido-1,3-Dimethylimidazolinium Chloride. *Synlett* **2010**, *2010*, 2503–2505, doi:10.1055/s-0030-1258568.
12. Nimnual, P.; Tummatorn, J.; Thongsornkleeb, C.; Ruchirawat, S. Utility of Nitrogen Extrusion of Azido Complexes for the Synthesis of Nitriles, Benzoxazoles, and Benzisoxazoles. *J Org Chem* **2015**, *80*, 8657–8667, doi:10.1021/acs.joc.5b01305.

 doi:10.20944/preprints202502.1105.v1

13. Shelke, A.; Bhong, B.; Karade, N. Oxidation of 1-Amidoalkyl-2-Naphthols Using (Diacetoxyiodo)Benzene: Unusual Formation of 1-Arylnaphtho[1,2-*d*]Isoxazoles. *Synthesis (Stuttg)* **2014**, *46*, 752–756, doi:10.1055/s-0033-1338590.
14. Chen, G.; Liu, H.; Li, S.; Tang, Y.; Lu, P.; Xu, K.; Zhang, Y. A Novel PPh 3 Mediated One-Pot Method for Synthesis of 3-Aryl or Alkyl 1,2-Benzisoxazoles. *Org. Lett.* **2017**, *19*, 1792–1795, doi:10.1021/acs.orglett.7b00563.
15. Van Eker, D.; Chauhan, J.; Murphy, W.A.; Conlon, I.L.; Fletcher, S. Chromatography-Free, Mitsunobu-Triggered Heterocyclizations of Salicylhydroxamic Acids to 3-Hydroxybenzisoxazoles. *Tetrahedron Lett.* **2016**, *57*, 5301–5303, doi:10.1016/j.tetlet.2016.10.045.
16. Cayley, A.; Gallagher, K.; Ménard-Moyon, C.; Schmidt, J.; Diorazio, L.; Taylor, R. Preparation of Novel Polycyclic Heterocycles Using a Tin(II) Chloride Dihydrate-Mediated Deacetalisation-Bicyclisation Sequence. *Synthesis (Stuttg)* **2008**, *2008*, 3846–3856, doi:10.1055/s-0028-1083214.
17. Modak, A.; Dutta, U.; Kancherla, R.; Maity, S.; Bhadra, M.; Mobin, S.M.; Maiti, D. Predictably Selective (sp3)C-O Bond Formation through Copper Catalyzed Dehydrogenative Coupling: Facile Synthesis of Dihydro-Oxazinone Derivatives. *Org. Lett.* **2014**, *16*, 2602–2605, doi:10.1021/ol500670h.
18. Whiting, E.; Lanning, M.E.; Scheenstra, J.A.; Fletcher, S. Chromatography-Free Entry to Substituted Salicylonitriles: Mitsunobu-Triggered Domino Reactions of Salicylaldoximes. *J. Org. Chem.* **2015**, *80*, 1229–1234, doi:10.1021/jo502396u.
19. Supsana, P.; Tsoungas, P.G.; Varvounis, G. A Novel One-Pot Synthesis of Isomeric Naphtho[1,2-*d*]Isoxazole 2-Oxide and Naphtho[1,8-*de*][1,2]Oxazine Ring Systems. A Case of Simultaneous *o*- and *Peri*-Cyclisation in Naphthalene. *Tetrahedron Lett.* **2000**, *41*, 1845–1847, doi:10.1016/S0040-4039(00)00029-0.
20. Supsana, P.; Tsoungas, P.G.; Aubry, A.; Skoulika, S.; Varvounis, G. Oxidation of 1-Acyl-2-Naphthol Oximes: Peri - and o -Cyclisation and Spiro Cyclodimerisation of Naphthoquinone Nitrosomethide Intermediates. *Tetrahedron* **2001**, *57*, 3445–3453, doi:10.1016/S0040-4020(01)00189-2.
21. Dolka, C.; Hecke, K. Van; Meervelt, L. Van; Tsoungas, P.G.; Eycken, E.V. Van der; Varvounis, G. Novel Thermal and Microwave-Assisted Facile Route to Naphthalen-2(1*H*)-Ones via an Oxidative Alkoxylation-Ring-Opening Protocol. *Org. Lett.* **2009**, *11*, 2964–2967, doi:10.1021/ol9008574.
22. Kozielewicz, P.; Tzeli, D.; Tsoungas, P.G.; Zloh, M. Arene-Fused 1,2-Oxazole N-Oxides and Derivatives. The Impact of the N–O Dipole and Substitution on Their Aromatic Character and Reactivity Profile. Can It Be a Useful Structure in Synthesis? A Theoretical Insight. *Struct. Chem.* **2014**, *25*, 1837–1846, doi:10.1007/s11224-014-0459-6.
23. Pal, S.; Khan, Md.N.; Karamthulla, S.; Choudhury, L.H. Synthesis of Pyranocoumarin Fused Spirooxindoles via Knoevenagel/Michael/Cyclization Sequence: A Regioselective Organocatalyzed Multicomponent Reaction. *Tetrahedron Lett.* **2015**, *56*, 359–364, doi:10.1016/j.tetlet.2014.11.095.
24. Tsoungas, G.P.; Cordopatis, P.; Gardikis, Y.; Potamitis, C.; Zervou, M. Xanthones in Heterocyclic Synthesis. An Efficient Route for the Synthesis of C-3 *o*-Hydroxyaryl Substituted 1,2-Benzisoxazoles and Their N-Oxides, Potential Scaffolds for Angiotensin(II) Antagonist Hybrid Peptides. *Heterocycles* **2011**, *83*, 1077, doi:10.3987/COM-11-12162.
25. Jadhav, V.K.; Deshmukh, A.P.; Wadagaonkar, P.P.; Salunkhe, M.M. Sodium Perborate: A Facile Synthesis of 1,2-Benzisoxazole 2-Oxides. *Synth. Commun.* **2000**, *30*, 1521–1527, doi:10.1080/00397910008087181.
26. Hesse, M.; Meier, H.; Zeeh, B. *Spectroscopic Methods in Organic Chemistry*; Hesse, M., Meier, H., Zeeh, B., Eds.; Georg Thieme Verlag: Stuttgart, 2008; ISBN 9783131060426.
27. Bracken, C.; Baumann, M. Development of a Continuous Flow Photoisomerization Reaction Converting Isoxazoles into Diverse Oxazole Products. *J. of Org. Chem.* **2020**, *85*, 2607–2617, doi:10.1021/acs.joc.9b03399.

 doi:10.20944/preprints202502.1105.v1

28. Belostotskaya, I.S.; Vol'eva, V.B.; Komissarova, N.L.; Dekaprilevich, M.O.; Khrustalev, V.N.; Karmilov, A.Yu.; Ershov, V. V. Oxidation of 2-Dialkylaminomethyl-4,6-Di-Tert-Butylphenols. *Russ. Chem. Bull.* **1997**, *46*, 1272–1280, doi:10.1007/BF02495927.
29. Maegawa, T.; Oishi, R.; Maekawa, A.; Segi, K.; Hamamoto, H.; Nakamura, A.; Miki, Y. The Reaction of Ketoximes with Hypervalent Iodine Reagents: Beckmann Rearrangement and Hydrolysis to Ketones. *Synthesis (Stuttg)* **2022**, *54*, 4095–4103, doi:10.1055/a-1835-2188.