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3,5-diarylisoxazoles: A New Entry to Soft Crystal Phase

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*This work describes the synthesis and characterization of a new liquid-crystalline compounds based on isoxazoles. Classical synthetic methodologies were employed in the preparation of this compounds, and the [3+2] 1,3-dipolar cycloaddition was the key step to prepare isoxazolines as precursors to isoxazoles. The structural and thermal characterization was performed using ^{1}H and ^{13}C NMR techniques, polarized-light optical microscopy and differential scanning calorimetry. Compounds **7a-e** displayed the SmA mesophase. Soft crystal phase (CrE) was observed for compounds **7a** and **7b** containing chlorine and bromine atoms. For **7e** containing a nitro group crystal phases below SmA mesophase were also observed.*

Keywords [3+2] 1; 3-dipolar cycloaddition; MnO_2 oxidation; soft crystal phase; CrE; liquid crystals

Introduction

The design and synthesis of new molecules with unique liquid crystals (LC) properties is a permanent challenge to the chemists. Many progresses have been done in this field, especially in the preparation of molecules with unusual molecular architecture beyond the classical calamitic- or discotic-shaped [1]. Among them, bent-core liquid crystals can be classified as unusual liquid crystals and they emerge as interesting class of LC with amazing behavior [2]. Usually bent-core mesogens have 1,3-phenylene unit connected by aromatics rings providing a 120° bent in the middle of the aromatic core [3].

Bent-shaped molecules are also founded in 5-membered heterocyclic if the bending angle varies between about 135° and 160°. In this sense molecules with this bending angle are more elongated in comparison to the 1,3-phenylene derivatives where the bending angle is 120° caused by the meta-substitution [4]. Typical mesophase formed by calamitic molecules, e.g N, SmA and SmC are observed when the bending angle increase to about 140° or more. So, the precise adjust of the molecular bent is crucial to reach the bent-core mesophases. Unfortunately, most of 5-membered heterocyclic used in the synthesis of new LC render calamitic mesophases [5] in despite of several synthetic efforts to change

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the topology - size, nature and shape - of the aromatic rings connected to the pentagonal heterocyclic.

However, we have to mention that when the bending angle approach to the 120° the possibility to reach optimal curvature of 1,3-phenylene core is greater. Thus, 2,5-disubstituted 1,3,4-oxadiazoles with a bending angle of *ca* 134° is one of the 5-membered heterocyclic ring that have gained attention of LC community because they are at the borderline between classical rod-like LCs and the bent-core mesogens [3]. Even the non-symmetric 3,5-disubstituted 1,2,4-oxadiazoles with a molecular bend of 140° have received attention due to their ferroelectric and biaxility behavior [6]. In this sense a number of new five-membered heterocyclic have been synthesized and the structural properties analyzed [7].

Less bent than 2,5-disubstituted 1,3,4-oxadiazoles or non-symmetric 3,5-disubstituted 1,2,4-oxadiazoles ring 3,5-disubstituted isoxazoles are real candidates to access highly ordered liquid crystals phase [8a] with potential applications in optical-electronic devices [8b-c]. Soft crystal mesophases are of great interest in electronic devices application since its organized structure next to a crystalline arrangement favors the intermolecular charge transport [8d].

Among the know strategy to prepare isoxazoles, [3+2] cycloaddition of 1,3-dipole to alkynes or indirectly to alkene followed by oxidation and condensation reaction of hydroxylamine with carbonyl compounds are the most important [9]. The interest in cycloaddition reaction of alkenes to 1,3-dipole has improved due to pharmacological properties of cycloadduct isoxazolines [10]. Isoxazolines are versatile precursors that readily undergoes further transformation e.g., alkylation [11], reductive cleavage [12] oxidation reaction to isoxazoles [13].

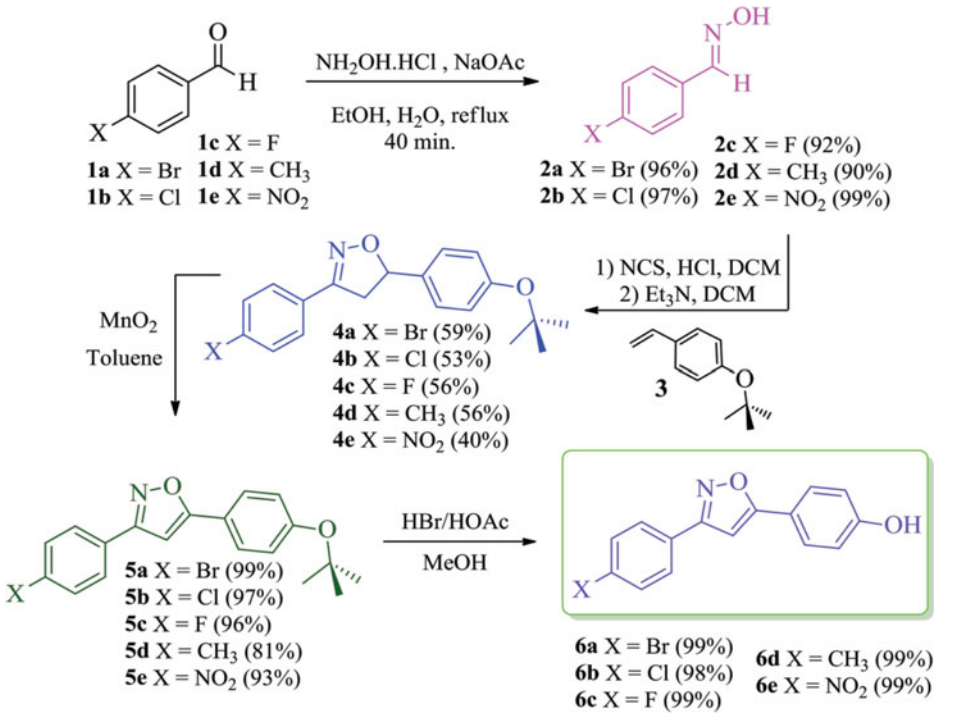
Our previous synthesis work related with design of new molecular architecture has shown that isoxazolines and isoxazoles serve as platform for new liquid-crystalline materials [14]. In this work we are extending our approach of new liquid crystals compounds by describing the synthesis and characterization of a series of new LC compounds based on the 3,5-disubstituted isoxazoles **7a-e**.

Results and Discussion

Synthesis

The sequential synthetic methodologies were employed in the preparation of isoxazoles core in this study. The Scheme I outlined the linear synthesis of isoxazoles **6a-e** in four steps. The [3+2] 1,3-dipolar cycloaddition of arylnitrile oxide with 4-*tert*-butoxystyrene as the key step in our synthetic plan to prepare the intermediate isoxazolines **4a-e** followed by MnO_2 oxidation to afford the protected phenol isoxazoles **5a-e** [13]. Benzaldehydes **1a-e** were chosen as starting materials to be transformed into oximes **2a-e** in high yields. Oximes are precursors for arylnitrile oxide, a reactive intermediate 1,3-dipoles for [3+2] cycloaddition. Solution of oximes were exposed to *N*-chlorosuccinimide (NCS) oxidant and the dipolarophile 4-*tert*-butoxystyrene (**3**), a masked phenol, to give the isoxazolines **4a-e** in moderate to good yields.

The one-pot reactions were carried out in the sequence (i) chlorination reaction of **2a-e** using *N*-clorosuccinimide and hydrochloride acid [15], in dichoromethane solution to yield the arylhydroximoyl chloride derivatives [16], (ii) addition of the dipholarofile, and

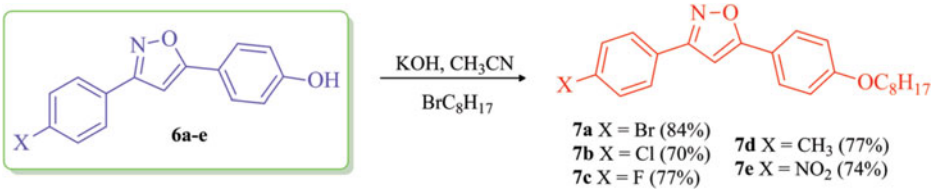


Scheme 1. Sequential synthetic route to obtain the phenol isoxazoles **6a-e.**

(iii) dehydrohalogenation reaction by addition of triethylamine for *in situ* generation of the reactive arylnitrile oxide.

The next step was the oxidation of isoxazolines to isoxazoles which was performed in toluene solution using activated MnO_2. Thus, the protected-isoxazoles **5a-e** were obtained in high yields by simple filtration of toluene solution over celite. After accomplished the transformation of isoxazolines into isoxazoles we proceed the remotion of *t*-butyl group from ether **5a-e** under acid condition - HBr/HOAc to give the phenols **6a-e** in quantitative yields [17].

The free phenols **6a-e** opens to us a new avenue to be explored in the liquid crystals field. Preliminary results in this sense has been done toward the preparation of polymethacrylate liquid-crystalline carrying the phenol **6a** where the liquid crystals behavior has been amplified and preserved by the polymerization reaction of the corresponding monomer [18].



Scheme 2. Alkylation reaction to afford the final liquid-crystalline compounds **7a-e**.

Table 1. Transition temperatures (°C) and enthalpies (kJ.mol^{-1}) on heating of the isoxazoles **7a-e**

Entry	X	Cr	Cr_1	Cr_2	CrE	SmA	N	I
7a [13]	Br	•		99 •	119	•		191 •
7b	Cl	•		96 (-) •	100 (16.4)*	•		190 (6.7) •
7c	F	•			97 (40.9)	•		154 (5.9) •
7d	CH_3	•			90 (35.8)	•	124 (0.9) •	141 (1.0) •
7e	NO_2	•	79 (7.8) •	101 (13.5) •	130 (13.4)	•		206 (4.7) •

*enthalpy value is the sum of the enthalpies of transitions Cr→CrE and CrE→SmA. The enthalpies are presented in brackets. Cr: crystal phase; CrE: soft crystal E; SmA: smectic A; N: nematic mesophase.

According to the Scheme II phenols **6a-e** were alkylated with 1-bromooctane with the formation of liquid-crystalline final compounds **7a-e**.

Liquid Crystal Properties

Transitional data are tabulated in Table 1 for all isoxazoles **7a-e**. Transition temperatures and enthalpy values were obtained by differential scanning calorimetry (DSC) and polarized-light optical microscopy (POM).

From Table 1 we can see that all LC isoxazoles synthesized displayed an enantiotropic behavior. DSC thermograms of **7b-e** are described in Figure 1 and all samples display a sharp and well-defined peaks associated with transitions temperatures for isoxazoles **7b-e**. The transition temperatures and enthalpy values were collected from second heating scans. The texture of the mesophase [19] was identified by microscopy studies. When the sample is cooled from its isotropic phase, the smectic A phase appears, which exhibited focal-conic texture. The stable enantiotropic smectic A phase was found in all the samples **7a-e**. For example, on heating the sample **7c** enters into the smectic A phase at 97°C and finally melts to an isotropic liquid at 154°C. The mesophase range for **7c** is 57°C. The two peaks observed at 97°C and 154°C were associated with Cr → SmA and SmA → I transitions, respectively, during the microscopy studies.

Similar behavior was observed to the last member containing the nitro group **7e**. As expected for more planar and anisotropic group, nitro substituent induce a large mesophase range ($\Delta T = 76°C$) and more stable mesophase behavior by comparison of clearing temperature between **7c** and **7e**. In fact, **7e** is the most stable LC in this study. Additionally, the compound **7e** showed two crystalline phase transitions probably due the intermolecular interactions of the nitro polar group [20].

For the **7a** and **7b**, along with SmA mesophase, on cooling, accompany another mesophase below transition from isotropic to SmA mesophase, with persistent continuous bands across the backs of the fans (Figure 2) for a long time. These changes are an indicative of a smectic A mesophase to a soft crystal phase E transition [19]. To these compounds **7a** and **7b** compounds the arced focal conic fan texture was assigned as crystal E phase (CrE). Our previous results showed that the 3,5-disubstituted isoxazoles are a good candidate to promotes the formation of a variety of soft LC phase which are under investigation and will be published soon [8a].

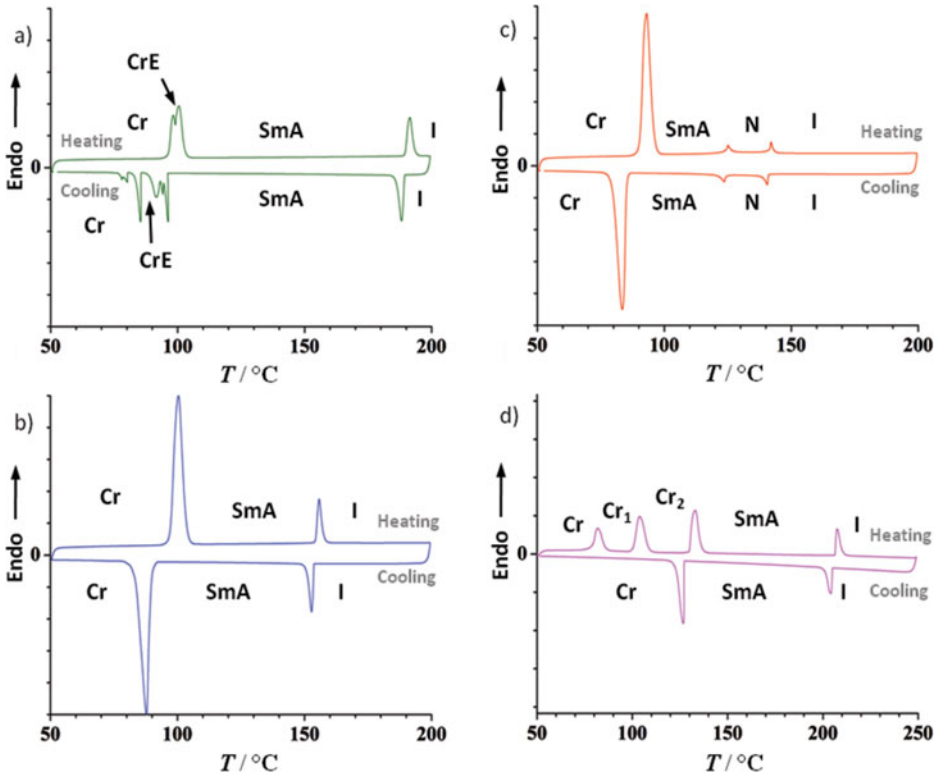


Figure 1. DSC curves of isoxazoles a) **7b**, b) **7c**, c) **7d** and d) **7e.**

LC **7c** with fluorine atom displayed only one orthogonal mesophase SmA and absence of any soft crystal phase or crystal to crystal transition. This particular behavior is related to the extreme electronegativity, size and lone pair of fluorine atom which result in both low atomic polarizability and small size [21].

Nematic mesophase was observed only for **7d** with mesophase range of the 14°C. In this series it can be seen that the less and small polar group favors the appearance

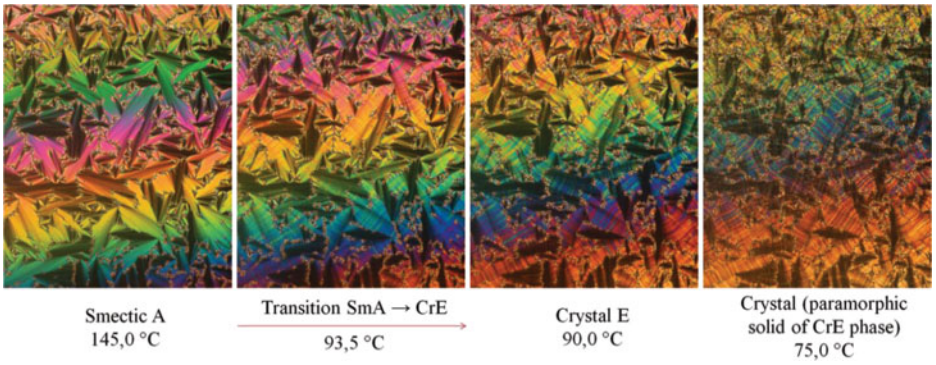


Figure 2. Textures observed by POM on cooling for compound **7b**.

nematic mesophase probably due to weak intermolecular interactions in the mesophase with predominance of Van der Waals attraction. All compounds in the series **7a-e** displayed the SmA mesophase, but only compounds containing chlorine and bromine atoms have a soft crystal E phase. Thus, this result is a good indication that there is a stronger correlation on the mesomorphic behavior concerning polar or steric effects of the substituent, since the compound containing fluorine atom **7c** neither with methyl group **7d** did not exhibit this mesophase. Results here are showing that a steric and polar effect that comes from large and polar group [22] are important parameters to be considered in the design of new liquid-crystal materials. The incorporation of larger and high polarizability atoms induce the formation of smectic phase and the appearance of CrE mesophases (soft crystal) [19], and they have a great impact on the size and shape of isoxazoles mesogens.

Conclusion

A series of 3,5-diarylisoxazoles liquid crystal **7a-e** were synthesized and mesomorphic properties were presented and discussed. [3+2] 1,3-dipolar cycloaddition and MnO_2-oxidation were used to prepare the hard core 3,5-disubstituted phenylisoxazoles **6a-e**. Alkylation reaction with linear alky bromides yielded the 3,5-diarylisoxazoles liquid crystal **7a-e**. Enantiotropic behavior was observed for all LC isoxazoles. For **7a** and **7b** containing terminal bromine and chlorine atoms displayed SmA phase and soft crystal phase (CrE). For **7c** having a terminal fluorine atom showed only SmA mesophase. LC isoxazole **7d** with a terminal methyl group presented a nematic mesophase along SmA mesophase. And finally, **7e** with a nitro group displayed only SmA mesophase. Additionally, upon heating, **7e** showed three crystal phase transition below SmA mesophase. Previous reported and this has showed that isoxazoles are key hard core to access a collection of new CL compounds with soft crystal phases.

Experimental Section

General

^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ were obtained using Varian Inova 300, Varian VNMRs 300 and Bruker Avance 400 spectrometers (Chemistry Institute – UFRGS). The coupling constants (J) are expressed by Hz and chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) used as internal standard. The thermal transitions and the textures were determined using an Olympus BX43 polarizing microscope in conjunction with a Mettler FP90 controller and HT84 heating stage and TA Instruments Q20 Serie Differential Scanning Calorimeter using ultra-pure N_2 gas at a flow rate of 50 mL.min^{-1} and the rate of heating or cooling was 10°C.min^{-1} without isotherms (LAMAT-UFRGS).

The reagents hydroxylamine hydrochloridrate, 4-bromobenzaldehyde, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, 4-methylbenzaldehyde, 4-nitrobenzaldehyde, 4-*tert*-butoxystyrene, *N*-chlorosuccinimide (NCS), 1-bromooctane, were used as received from Aldrich Co. Analytical. Thin Layer Chromatography (TLC) was conducted on Merck aluminium plates with 0.2mm of silica gel 60F-254. Anhydrous sodium sulfate was used to dry all organic extracts. All other solvents and reagents were used without previous purification.

Procedures

Synthesis of aldoximes 2a-e. Representative procedure for compound **2a**. In a round bottom flask to a solution of 4-chlorobenzaldehyde (5.00 g, 35.57 mmol) in ethanol (135 mL) was added hydroxylamine hydrochloride (6.92 g, 99.60 mmol) and a solution of sodium acetate (11.67 g, 142.28 mmol) in water (70 mL). The mixture was stirred under reflux for 40 minutes, ethanol was removed by heat and vacuum. The concentrate was crystallized on freezer overnight to give the pure product.

Data for 4-bromobenzaldehyde oxime (**2a**): white crystalline solid; yield: 96%; m.p. 109–111°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.12 (s, 1H), 7.51 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.7, 132.3, 131.0, 128.7, 124.6.

Data for 4-chlorobenzaldehyde oxime (**2b**): white crystalline solid; yield: 97%; m.p. 101–103°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.52 (m, 2H), 7.36 (m, 2H).

Data for 4-fluorobenzaldehyde oxime (**2c**): white crystalline solid; yield: 92%; m.p. 84–86°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.17 (s, 1H), 7.59 (m, 2H), 7.11 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.8 (d, $^1J_{C\text{-}F} = 250.5$ Hz), 149.5, 129.0 (d, $^3J_{C\text{-}F} = 8.4$ Hz), 128.0 (d, $^4J_{C\text{-}F} = 3.4$ Hz), 116.0 (d, $^2J_{C\text{-}F} = 22.1$ Hz).

Data for 4-methylbenzaldehyde oxime (**2d**): pink pale solid; yield: 90%; m.p. 68–70°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.38 (m, 2H), 7.09 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.3, 140.3, 129.5, 129.0, 127.0, 21.4.

Data for 4-nitrobenzaldehyde oxime (**2e**): Yellow solid; yield: 99%; m.p. 127–129°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (m, 2H), 8.21 (s, 1H), 8.11 (s, 1H), 7.76 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$/DMSO d^6) δ 147.7, 146.8, 139.0, 127.1, 123.6.

Synthesis of isoxazolines 4a-e (Cycloaddition [3+2] 1,3-Dipolar). Representative procedure for compound **4d**. In a round bottom flask, were added 4-methylbenzaldehyde oxime (**2d**) (2.03 g, 15.00 mmol), *N*-chlorossuccinimide (2.20 g, 16.50 mmol), dichloromethane (45 mL) and a drop of HCl_{conc}, the mixture was stirred for 4 hours to form the oximoyl chloride. After the formation of the intermediate the mixture was cooled in ice bath, and to the solution were added 4-*tert*-butoxystyrene (**3a**) (2.82 mL, 15.00 mmol) and triethylamine (6.27 mL, 45.00 mmol) dropwise, then the mixture was stirred at room temperature for 24 hours. After the reaction time the mixture was washed with 1M HCl (2 × 20 mL) and brine (2 × 20 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure giving the crude material. The product was purified by recrystallization in ethanol.

Data for 3-(4-bromophenyl)-5-(4-(*tert*-butoxy)phenyl)isoxazoline (**4a**): white crystalline solid; yield: 59%; m.p. 121–123°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.28 (m, 2H), 6.99 (m, 2H), 5.70 (dd, 1H, $^3J_{cis} = 11.1$ Hz, $^3J_{trans} = 8.7$ Hz), 3.71 (dd, 1H, $^2J_{gem} = 16.8$ Hz, $^3J_{cis} = 11.1$ Hz), 3.31 (dd, 1H, $^2J_{gem} = 16.8$ Hz, $^3J_{trans} = 8.7$ Hz), 1.34 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5, 155.4, 135.12, 131.9, 128.5, 128.1, 126.7, 126.6, 124.3, 82.7, 78.7, 42.7, 28.8.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-chlorophenyl)isoxazoline (**4b**): white crystalline solid; yield: 53%; m.p. 135–136°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.38 (m, 2H), 7.28 (m, 2H), 6.99 (m, 2H), 5.71 (dd, 1H, $^3J_{cis} = 10.9$ Hz, $^3J_{trans} = 8.8$ Hz), 3.71 (dd, 1H, $^2J_{gem} = 16.8$ Hz, $^3J_{cis} = 11.1$ Hz), 3.32 (dd, 1H, $^2J_{gem} = 16.8$ Hz, $^3J_{trans} = 8.7$ Hz), 1.35 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 155.7$, 155.5, 136.1, 135.3, 129.1, 128.2, 128.1, 126.8, 124.5, 82.9, 78.9, 42.9, 29.0.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-fluorophenyl)isoxazoline (**4c**): white crystalline solid; yield: 55%; m.p. 139–140°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 2H),

7.29 (m, 2H), 7.09 (m, 2H), 6.99 (m, 2H), 5.70 (dd, 1H, $^{3}J_{cis} = 10.9$ Hz, $^{3}J_{trans} = 8.6$ Hz), 3.72 (dd, 1H, $^{2}J_{gem} = 16.7$ Hz, $^{3}J_{cis} = 10.9$ Hz), 3.33 (dd, 1H, $^{2}J_{gem} = 16.7$ Hz, $^{3}J_{trans} = 8.6$ Hz), 1.34 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.7 (d, $^{1}J_{C\text{-}F} = 250.7$ Hz), 155.5, 155.3, 135.3, 128.6 (d, $^{3}J_{C\text{-}F} = 8.3$ Hz), 126.7, 125.8 (d, $^{4}J_{C\text{-}F} = 3.1$ Hz), 124.3, 115.8 (d, $^{2}J_{C\text{-}F} = 21.8$ Hz), 82.6, 78.7, 43.0, 28.8.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-methylphenyl)isoxazoline (**4d**): White solid; yield: 56%; m.p. 106–108°C; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.59$ (m, 2H), 7.29 (m, 2H), 7.21 (m, 2H), 6.98 (m, 2H), 5.65 (dd, 1H, $^{3}J_{cis} = 11.0$ Hz, $^{3}J_{trans} = 8.6$ Hz), 3.72 (dd, 1H, $^{2}J_{gem} = 16.7$ Hz, $^{3}J_{cis} = 11.0$ Hz), 3.33 (dd, 1H, $^{2}J_{gem} = 16.7$ Hz, $^{3}J_{trans} = 8.6$ Hz), 2.37 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 156.3$, 155.4, 140.5, 135.7, 129.6, 126.9, 126.8, 124.5, 82.4, 78.8, 43.2, 29.0, 21.6.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-nitrophenyl)isoxazoline (**4e**): Light yellow solid; yield: 40%; m.p. 143°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (m, 2H), 7.86 (m, 2H), 7.28 (m, 2H), 7.50 (m, 2H), 5.79 (dd, 1H, $^{3}J_{cis} = 11.1$ Hz, $^{3}J_{trans} = 8.7$ Hz), 3.77 (dd, 1H, $^{2}J_{gem} = 16.8$ Hz, $^{3}J_{cis} = 11.1$ Hz), 3.38 (dd, 1H, $^{2}J_{gem} = 16.8$ Hz, $^{3}J_{trans} = 8.7$ Hz), 1.34 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8, 154.7, 148.4, 135.6, 134.5, 127.3, 126.6 124.3, 124.0, 83.6, 78.8, 42.2, 28.8.

Synthesis of isoxazoles 5a-e (Oxidation Reaction). Representative procedure for **5a**. In a round bottom flask were added isoxazoline **4a** (0.50 g, 1.34 mmol), toluene (25 mL) and MnO_2 (1.75 g, 20.13 mmol), the reaction was carried under azeotropic reflux overnight. After consumption of starting material the mixture was cooled down and filtered over a plug of celite and washed with CH_2Cl_2. The solvent was removed under reduced pressure giving the product.

Data for 3-(4-bromophenyl)-5-(4-(*tert*-butoxy)phenyl)isoxazole (**5a**): white crystalline solid; yield: 99%; m.p. 157–158°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.59 (m, 2H), 7.08 (m, 2H), 6.69 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.6, 161.9, 157.6, 132.1, 128.2, 126.8, 124.2, 126.7, 123.9, 122.0, 96.3, 79.4, 28.8.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-chlorophenyl)isoxazole (**5b**): white crystalline solid; yield: 97%; m.p. 151–152°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.71 (m, 2H), 7.41 (m, 2H), 7.08 (m, 2H), 6.68 (s, 1H), 1.39 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5, 161.8, 157.6, 135.8, 129.1, 128.0, 127.6, 126.7, 123.8, 122.0, 96.4, 79.4, 28.8.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-fluorophenyl)isoxazole (**5c**): white crystalline solid; yield: 96%; m.p. 146–147°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.74 (m, 2H), 7.16 (m, 2H), 7.09 (m, 2H), 6.70 (s, 1H), 1.41 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5, 163.7 (d, $^{1}J_{C\text{-}F} = 249.7$ Hz), 162.0, 157.6, 128.7 (d, $^{3}J_{C\text{-}F} = 8.6$ Hz), 126.8, 125.4 (d, $^{4}J_{C\text{-}F} = 3.1$ Hz), 124.0, 122.2, 116.0 (d, $^{2}J_{C\text{-}F} = 21.8$ Hz), 96.4, 79.5, 28.9.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-methylphenyl)isoxazole (**5d**): white solid; yield: 80%; m.p. 111–112°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.21 (m, 2H), 7.05 (m, 2H), 6.67 (s, 1H), 2.35 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 162.7, 157.3, 139.8, 129.4, 126.5, 126.21, 123.7, 122.2, 96.5, 96.4, 79.1, 28.7, 21.3.

Data for 5-(4-(*tert*-butoxy)phenyl)-3-(4-nitrophenyl)isoxazole (**5e**): yellow crystalline solid, yield: 95%; m.p. 180–182°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (m, 2H), 8.04 (m, 2H), 7.75 (m, 2H), 7.36 (benzene), 7.11 (m, 2H), 6.79 (s, 1H), 1.42 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.4, 164.7, 158.0, 148.7, 135.4, 127.6, 126.9, 124.2, 123.9, 121.7, 96.5, 79.5, 28.9.

Synthesis of Phenols 6a-e. (Hydrolysis). Representative procedure for **6c**. A solution of isoxazole **5c** (0.75 g, 2.41 mmol), methanol (54 mL), glacial acetic acid (1.79 mL,

31.33 mmol), HBr_{conc} (3.55 mL, 31.33 mmol) was stirred under reflux for 4–6 hours. After the consumption of starting material (followed by TLC) the mixture was cooled to room temperature and neutralized to pH∼6 with saturated solution of $NaHCO_3$, the product was precipitated and filtered off, giving a pure product.

Data for 3-(4-bromophenyl)-5-(4-hydroxyphenyl)isoxazole (**6a**): beige solid; yield: 99%; m.p. 204–206°C; ^{1}H NMR (300 MHz, $CDCl_3$, 3 drops of DMSO d^6) δ 9.48 (s, 1H), 7.73 (m, 2H), 7.67 (m, 2H), 7.60 (m, 2H), 6.95 (m, 2H), 6.68 (s, 1H), 2.83 (water); ^{13}C NMR (75.5 MHz, $CDCl_3$, 3 drops of DMSO d^6) δ 170.7, 164.4, 161.5, 159.2, 131.7, 127.9, 127.1, 123.6, 118.2, 115.8, 95.0.

Data for 3-(4-chlorophenyl)-5-(4-hydroxyphenyl)isoxazole (**6b**) : white solid; yield: 99%; m.p. 201–203°C; ^{1}H NMR (300 MHz, acetone d^6) δ 7.94 (m, 2H), 7.77 (m, 2H), 7.55 (m, 2H), 7.18 (s, 1H), 7.01 (m, 2H); ^{13}C NMR (75.5 MHz, acetone d^6) δ 171.9, 162.7, 160.6, 136.2, 130.1, 129.3, 129.2, 128.4, 120.0, 116.9, 96.8.

Data for 3-(4-fluorophenyl)-5-(4-hydroxyphenyl)isoxazole (**6c**) : white solid; yield: 99%; m.p. 209–210°C; ^{1}H NMR (300 MHz, acetone d^6) δ 7.99 (m, 2H), 7.78 (m, 2H), 7.29 (m, 2H), 7.16 (s, 1H), 7.02 (m, 2H); ^{13}C NMR (75.5 MHz, acetone d^6) δ 171.7, 164.5 (d, $^1J_{C\text{-}F} = 247.7$ Hz), 162.7, 160.6, 129.7 (d, $^3J_{C\text{-}F} = 8.5$ Hz), 128.3, 126.8 (d, $^4J_{C\text{-}F} = 3.1$ Hz), 119.8, 116.9, 116.7 (d, $^2J_{C\text{-}F} = 22.0$ Hz), 96.7.

Data for 5-(4-hydroxyphenyl)-3-(4-methylphenyl)isoxazole (**6d**): pink pale solid; yield: 99%; m.p. 179–181°C; ^{1}H NMR (300 MHz, acetone d^6) δ 7.80 (m, 4H), 7.33 (d, 2H, $J = 8.4$ Hz), 7.12 (s, 1H), 7.00 (d, 2H, $J = 8.7$ Hz), 2.39 (s, 3H); ^{13}C NMR (75.5 MHz, acetone d^6) δ 171.4, 163.6, 160.4, 140.9, 130.5, 128.4, 127.7, 127.5, 120.2, 116.9, 96.7, 21.4.

Data for 5-(4-hydroxyphenyl)-3-(4-nitrophenyl)isoxazole (**6e**): yellow solid; yield: 90%; m.p. 240–242°C; ^{1}H NMR (300 MHz, acetone d^6) δ 8.40 (m, 2H), 8.22 (m, 2H), 7.80 (m, 2H), 7.32 (s, 1H), 7.03 (m, 2H); ^{13}C NMR (75.5 MHz, acetone d^6) δ 172.5, 162.1, 160.9, 149.7, 136.5, 128.6, 128.4, 125.0, 119.5, 117.0, 97.1.

Synthesis of isoxazoles 7a-e (Alkylation Reaction). Representative procedure for compound **7e**. In a round bottom two-necked flask fitted with reflux condenser, were added phenol **6e** (0.40 g, 1.42 mmol), acetonitrile (6 mL) and potassium hydroxide (0.09 g, 1.56 mmol). The mixture was heated at 90°C until homogeneous. After that 1-bromooctane (0.28 mL, 1.56 mmol) was added dropwise and the reaction mixture was stirred under reflux for 4–6 hours (followed by TLC). At the end of the reaction the solvent was evaporated, added CH_2Cl_2 (10 mL) and the mixture was washed with H_2O (2 × 5 mL), $NaHCO_3$ (2 × 5 mL) and $NaCl_{sat}$ (2 × 5 mL). The organic phase was dried with Na_2SO_4 and, after filtration, the solvent was evaporated. The crude material was recrystallized in ethanol.

Data for 3-(4-bromophenyl)-5-(4-(octyloxy)phenyl)isoxazole (**7a**): white solid; yield: 84%; Transition temperatures: **Cr** 99°C **CrE** 119°C **SmA** 191°C **I**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.60 (d, 2H, $J = 8.4$ Hz), 6.97 (d, 2H, $J = 8.6$ Hz), 6.66 (s, 1H), 4.00 (t, 2H), 1.81 (m, 2H), 1.55–1.10 (m, 14H), 0.88 (t, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.3, 170.8, 161.9, 160.8, 132.1, 128.3, 128.2, 127.4, 124.1, 119.8, 114.9, 95.7, 68.2, 31.9, 29.6, 29.4, 29.3, 29.1, 26.0, 22.7, 14.1.

Data for 3-(4-chlorophenyl)-5-(4-(octyloxy)phenyl)isoxazole (**7b**): white solid; yield: 70%; Transition temperatures: **Cr** 96°C **CrE** 100°C **SmA** 190°C **I**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (m, 4H), 7.45 (d, 2H, $J = 8.4$ Hz), 6.98 (d, 2H, $J = 8.8$ Hz), 6.66 (s, 1H), 4.01 (t, 2H, $J = 6.4$ Hz), 1.84–1.77 (m, 2H), 1.50–1.23 (m, 10H), 0.89 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 161.9, 160.9, 135.9, 129.2, 128.1,

127.8, 127.4, 119.8, 114.9, 95.8, 68.2, 31.8, 29.4, 29.3, 29.2, 26.0, 22.7, 14.1; EA, calc. for $C_{23}H_{26}ClNO_2$, 383.91 g/mol:, C 71.96, H 6.83, N 3.65, found: C 72.59, H 6.90, N 3.66.

Data for 3-(4-fluorophenyl)-5-(4-(octyloxy)phenyl)isoxazole (**7c**): white solid; yield: 77%; Transition temperatures: **Cr** 97°C **SmA** 154°C **I**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.67 (m, 2H), 7.09 (m, 2H), 6.91 (m, 2H), 6.58 (s, 1H), 3.93 (t, 2H, $J = 6.6$ Hz), 1.73 (m, 2H), 1.46–1.12 (m, 10H), 0.82 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.6, 163.7 (d, $^1J_{C\text{-}F} = 249.7$ Hz), 161.9, 160.8, 128.6 (d, $^3J_{C\text{-}F} = 8.5$ Hz), 127.4, 125.6 (d, $^4J_{C\text{-}F} = 3.3$ Hz), 119.8, 115.9 (d, $^2J_{C\text{-}F} = 21.9$ Hz), 114.9, 95.8, 68.2, 31.8, 29.3, 29.2, 29.1, 26.0, 22.6, 14.1; EA, calc. for $C_{23}H_{26}FNO_2$, 367.46 g/mol:, C 75.18, H 7.13, N 3.81, found: C 75.13, H 7.21, N 3.80.

Data for 3-(4-methylphenyl)-5-(4-(octyloxy)phenyl)isoxazole (**7d**): white solid; yield: 77%; Transition temperatures: **Cr** 90°C **SmA** 124°C **N** 141°C **I**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 4H), 7.27 (d, 2H, $J = 8.0$ Hz), 6.97 (d, 2H, $J = 8.8$ Hz), 6.67 (s, 1H), 4.00 (t, 2H, $J = 6.4$ Hz), 2.41 (s, 1H), 1.84–1.77 (m, 2H), 1.50–1.23 (m, 10H), 0.89 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.3, 162.8, 160.7, 140.0, 129.5, 127.3, 126.7, 126.4, 120.1, 114.9, 95.9, 68.2, 31.8, 29.3, 29.2, 29.1, 26.0, 22.7, 21.4, 14.1; EA, calc. for $C_{24}H_{29}NO_2$, 363.49 g/mol:, C 79.30, H 8.04, N 3.85, found: C 79.00, H 8.05, N 3.88.

Data for 3-(4-nitrophenyl)-5-(4-(octyloxy)phenyl)isoxazole (**7e**): light yellow solid; yield: 74%; Transition temperatures: **Cr** 79°C **Cr$_1$** 101°C **Cr$_2$** 130°C **SmA** 206°C **I**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.03 (m, 2H), 7.76 (m, 2H), 6.99 (m, 2H), 6.75 (s, 1H), 4.01 (t, 2H, $J = 6.6$ Hz), 1.81 (m, 2H), 1.54–1.19 (m, 10H), 0.89 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.6, 161.2, 161.1, 148.7, 135.5, 127.7, 127.6, 124.3, 119.5, 115.1, 96.0, 68.4, 31.9, 29.5, 29.4, 29.3, 26.1, 22.8, 14.2; EA, calc. for $C_{23}H_{26}N_2O_4$, 394.46 g/mol:, C 70.03, H 6.64, N 7.10, found: C 70.52, H 6.72, N 7.14..

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