



# 1,3-Dipolar cycloaddition reaction applied to synthesis of new unsymmetric liquid crystal compounds-based isoxazole

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## ABSTRACT

In this study, a regioselective, simple and versatile copper(I)-catalyzed procedure for preparation of a series of liquid crystals based on unsymmetrical 3,5-disubstituted isoxazole was developed. Using different substituted chloro oximes and phenyl acetylenes, 1,3-dipolar cycloaddition reaction was carried out. A second series containing the isoxazole ring and a triple bond in the rigid core was also synthesized. From the 3-(4-bromophenyl)-5-(4-(decyloxy)phenyl)isoxazole, new liquid-crystalline compounds were prepared by Sonogashira cross-coupling. All of the derivatives of the isoxazole ring compounds exhibited mesomorphism. Smectic C, smectic A, and nematic phases were observed by optical microscopy and DSC analysis. The yield of these reactions varied from moderate to excellent (47–93%). The structure of the rigid core was investigated by single crystal X-ray diffraction, which confirmed the regioselectivity of the [3+2] dipolar cycloaddition reaction.

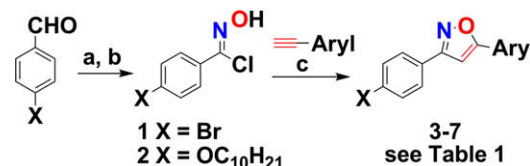
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## 1. Introduction

Liquid crystal compounds have found application in widespread scientific and technological areas, especially as flat-panel displays,<sup>1</sup> light emitting diodes (OLEDs),<sup>2</sup> anisotropic networks,<sup>3</sup> photoconductors, and semiconductor materials.<sup>4</sup> Numerous liquid-crystalline compounds have been synthesized with a wide variety of shapes, the most popular being the rod-like shape, also called calamitic.<sup>5</sup> The calamitic liquid crystals are a well-known class that shows typical smectic and nematic mesophases derived from the self-organization of their anisometric units. During the past decades, a large number of liquid-crystalline compounds containing heterocyclic units have been synthesized.<sup>5</sup> This research field has grown even more in the recent years because of improvements in synthetic methodologies. The interest in such compounds arises from the fact that the incorporation of heteroatoms can result in large changes in the corresponding liquid-crystalline phases and/or in the physical properties of the observed phases because most of the usual heteroatoms (S, O, and N) introduced are chemically classified as more polarizable than carbon.<sup>6</sup> Unsymmetrical 3,5-disubstituted isoxazole liquid-crystalline compounds can be introduced into the class of calamitic molecules. However, to the best of our knowledge, little detailed research on the relationships between structure and mesomorphic properties of unsymmetrical 3,5-disubstituted isoxazole derivative has been reported.

Several methods have been adopted for the synthesis of unsymmetrical 3,5-disubstituted isoxazoles, including approaches based on condensation of 1,3-dicarbonyl compounds with hydroxylamine<sup>7</sup> (which have been isolated as equal mixtures of two regioisomers), anchoring a nitrile oxide precursor onto the solid phase,<sup>8</sup> condensations,<sup>9</sup> and intramolecular cyclization of amino acids.<sup>10</sup> These procedures have often exhibited quite low yields, side reactions result in impurities, and both regioisomers are often obtained.

In particular, nitrile oxides which undergo efficient [3+2] cycloaddition with terminal alkynes can be a convenient protocol to the synthesis of isoxazoles. However, a survey of the literature showed that 1,3-dipolar cycloadditions reaction between dipolarophiles derived from activated alkynes and nitrile oxides generally resulted in moderate yields and low regioselectivity. Further, the use of catalysts in 1,3-dipolar cycloaddition of nitrile oxides and alkynes permitted significant improvements, especially concerning yields and regioselectivity, that in general are quite low in uncatalyzed processes.<sup>11,12</sup> Thus, within this topic, a very important reac-



**Scheme 1.** Reagents: (a) NH<sub>2</sub>OH·HCl, KOH, CH<sub>3</sub>CH<sub>2</sub>OH/H<sub>2</sub>O; (b) DMF, NCS; (c) CuI, KHCO<sub>3</sub>, *t*-butanol/THF.

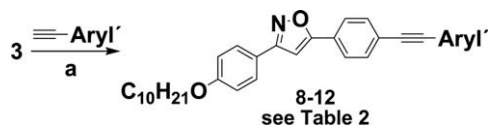
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**Table 1**  
Yields for 1,3-cycloaddition reaction of **3–7** and their mesomorphic behavior

Entry	X	Aryl <sup>a</sup>	Yield	Transition temperatures (°C) <sup>b</sup>
3	Br		84	Cr 99 SmC 114 SmA184 I
4	OC <sub>10</sub> H <sub>21</sub>		74	Cr 105 N 186 I
5	OC <sub>10</sub> H <sub>21</sub>		62	Cr 117 SmA 136 N 238 I
6	OC <sub>10</sub> H <sub>21</sub>		72	Cr 93 N 134 I
7	OC <sub>10</sub> H <sub>21</sub>		50	Cr 130 SmA 244 I

<sup>a</sup> R = OC<sub>10</sub>H<sub>21</sub>.

<sup>b</sup> Cr = crystal phase; SmA = smectic A; SmC = smectic C; N = nematic phase; I = isotropic.



**Scheme 2.** Reagents: (a) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, PPh<sub>3</sub>, THF/TEA.

**Table 2**  
Yields for Sonogashira cross-coupling of **8–12** and their mesomorphic behavior

Entry	Aryl <sup>a</sup>	Yield%	Transition temperatures <sup>b</sup> (°C)
8		66	Cr 125 SmC 220 N 240 I
9		93	Cr 135 SmA 234 N 274 I
10		74 <sup>c</sup>	Cr 173 N 310 I
11		47 <sup>c</sup>	Cr 130 SmC 266 N 316 I
12		75 <sup>c</sup>	Cr 136 SmC 300 I

<sup>a</sup> R = OC<sub>10</sub>H<sub>21</sub>.

<sup>b</sup> Cr = crystal phase; SmA = smectic A; SmC = smectic C; N = nematic phase; I = Isotropic.

<sup>c</sup> Yields obtained using pyridine as solvent.

tion is the 1,3-dipolar cycloaddition mediated by Cu(I). This methodology enables the preparation of unsymmetrical 3,5-disubstituted isoxazoles with specific regioselectivity.

In this Letter, we report a convenient procedure for the regioselective synthesis of unsymmetrical 3,5-disubstituted isoxazoles from alkynes and imidoyl chloride catalyzed by Cu(I). Several aryl acetylenes were reacted with imidoyl chloride to give new liquid crystal derivatives from isoxazoles.

Using the same rigid core system, (**3**) was reacted again with the terminal alkynes via Sonogashira coupling to give a second series.

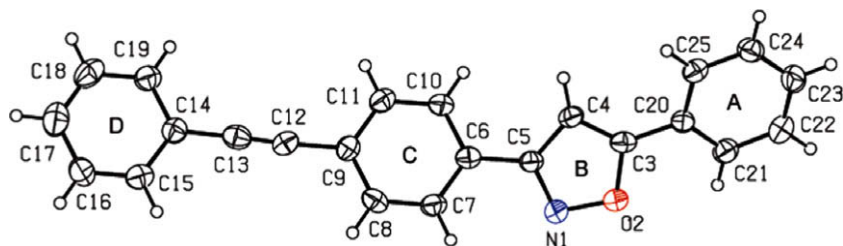
## 2. Results and discussion

The strategy for the synthesis of the final compounds is outlined in [Scheme 1](#).

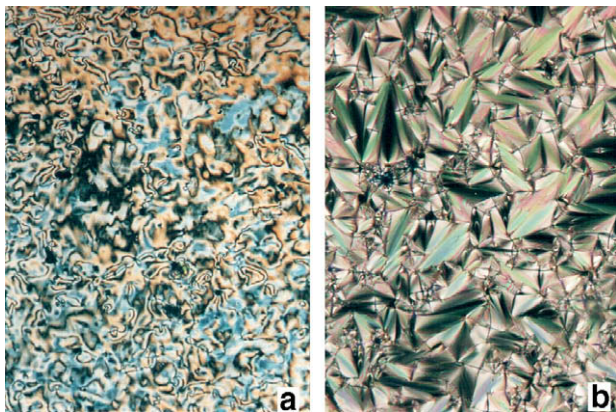
The first step was the synthesis of the oxime intermediates from 4-(decyloxy)benzaldehyde or 4-(bromo) benzaldehyde using hydroxylamine chloride and potassium hydroxide in an ethanol/water mixture at room temperature. The respective aldoximes were transformed to the corresponding *N*-hydroxybenzimidoyl chlorides (**1** and **2**) with *N*-chlorosuccinimide in dimethylformamide. Several terminal aryl acetylenes with distinct electronic-systems were also prepared. The alkynes were prepared according to the literature<sup>13</sup> from different aryl bromides by palladium catalyzed with 2-methyl-3-butyn-2-ol (Sonogashira coupling reaction) followed by protective group elimination. The 3,5-disubstituted isoxazoles were obtained by 1,3-dipolar cycloaddition reaction between an appropriately substituted chloro oxime and an aryl acetylene. Starting from the freshly prepared 4-bromo-*N*-hydroxybenzimidoyl chloride (**1**), the nitrile oxide was best obtained in situ (from the corresponding aldoximes by oxidative halogenation/dehydrohalogenation) and reacted with the 1-(decyloxy)-4-ethynylbenzene with a catalytic amount of copper (I) iodine (5 mol %) and potassium bicarbonate in an ethanol/water mixture,<sup>14</sup> affording compound **3**. The general procedure was applied to obtain the final compounds **4–7**, but by using 4-(decyloxy)-*N*-hydroxybenzimidoyl chloride (**2**) and the respective aryl acetylene. All of the cycloaddition reactions were carried out at room temperature. Compounds **3–7** showed liquid-crystalline properties, compound **3** being the precursor for compounds **8–12**. The reaction yields for the 1,3-cycloaddition reactions are shown in [Table 1](#).

The target compounds **8–12** were synthesized from **3** as outlined in [Scheme 2](#).

Bromide **3** was used as the building block for construction of the carbon-carbon triple bond. The reactions were carried out through Sonogashira cross-coupling with different aryl acetylenes<sup>15</sup> (see [Table 2](#)). These reactions employed 10% dichlorobis(triphenylphosphine)palladium as the catalyst, 5 mol % of the co-catalyst cop-



**Figure 1.** Molecular structure of compound **14**. Torsion angle values for planes A and B = 25.2(1)°; B and C 25.3(1)°; and C and D 4.6(2)°.



**Figure 2.** Photomicrographs (33 $\times$ ) of compound **9** showing: (a) *Schlieren* texture of N phase at 235 °C; and (b) focal-conic fan-shaped texture of SmA phase at 140 °C upon cooling. Samples were sandwiched between untreated glass slides and viewed through crossed polarizers.

per(I) iodine, and triphenylphosphine as an additive in a triethylamine/tetrahydrofuran mixture (1:3) under reflux. As expected, these compounds also showed mesomorphic behavior. The reaction yields for the Sonogashira reaction products **8–12** are presented in Table 2.

However, using the same procedure for compounds **10**, **11**, and **12** only traces of the desired compounds were obtained with a considerable amount of homo-coupling product. This finding had been previously reported by our group in the synthesis of similar molecules,<sup>16</sup> and thus in the synthetic route of these final compounds the functionalities need to be reversed. In this reaction, the Sonogashira coupling of the aryl acetylenes was used to build the triple bond terminal in compound **3**, and the intermediary 5-(4-(decyloxy)phenyl)-3-(4-ethynylphenyl) isoxazole (**13**) was obtained with 76% global yield. Finally, the target compounds **10**, **11**, and **12** were obtained by reaction of aryl acetylene **13** with the respective aryl bromide via Sonogashira coupling. The yields of these reactions were low (17–30%). The reaction was therefore repeated using pyridine as the solvent<sup>17</sup>, and the yields increased to 74%, 47%, and 75%, respectively.

In order to analyze the rigid core and, particularly, the regioselectivity of these 1,3-cycloaddition reactions catalyzed by Cu(I), we tried to obtain a single crystal of the final compounds synthesized. Due to the difficulty in obtaining good single crystals, a 3,5-disubstituted isoxazole derivative without terminal chains, 5-phenyl-3-[4-(phenylethynyl) phenyl]isoxazole (**14**), was also prepared (Fig. 1). This compound was synthesized from 3-(4-bromophenyl)-5-phenylisoxazole, prepared from compound **1** with phenylacetylene by 1,3-dipolar cycloaddition reaction, and subsequent Sonogashira reaction with the same acetylene, in 56% yield. Yellow single crystals of **14** suitable for X-ray analysis were obtained by recrystallization from chloroform.<sup>18</sup>

The structure of compound **14** clearly shows the regioselectivity of the 1,3-dipolar cycloaddition reaction mediated by Cu(I). The molecular geometry of the molecule under discussion is not planar but consists of structural fragments (benzene and isoxazole rings) with more or less perfect planarity (Fig. 1). The overall molecular conformation results from the dihedral angles between these fragments observed from the crystallographic data on the structures (see Supplementary data).

The structures of all of the synthesized compounds were fully characterized by IR, <sup>1</sup>H and <sup>13</sup>C NMR, and CHN mass analyses.

A brief study of the mesomorphism of the final molecules **3–7** and **8–12** was performed using polarizing optical microscopy (POM) and the results are shown in Tables 1 and 2. All of the compounds prepared exhibited mesophases characteristic of calamitic liquid crystal, that is, smectic C (SmC) and nematic (N) phases, with *Schlieren* textures, and smectic A (SmA) with the focal-conic fan-shaped texture. Compounds **8**, **9**, and **11** showed dimorphism of SmC and N phases, and compound **3** of SmA and N phases. The characteristic textures of the calamitic liquid crystal are shown in Figure 2. Compounds **4**, **6**, **7**, **10**, and **12** presented only nematic or smectic phase.

### 3. Conclusions

In conclusion, a regioselective, simple and convenient copper(I)-catalyzed procedure for preparation of liquid crystals based on unsymmetrical 3,5-disubstituted isoxazole was developed. Using different substituted chloro oximes and aryl acetylenes, which were obtained by 1,3-dipolar cycloaddition reaction, a series of liquid crystals based on isoxazole was reported. A second series containing the isoxazole ring and triple bond in the rigid core was also synthesized by Sonogashira cross-coupling. The final materials **4–7** and **8–12** were obtained in moderate to good yields (47–93%). These compounds showed liquid-crystalline behavior with a varied polymorphic SmC, SmA, and N phases.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.021.

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14. *General procedure to [3+2] dipolar cycloadditions*: To a 50 mL round-bottomed flask 1-(decyloxy)-4-ethynylbenzene (1.0 g, 5.5 mmol), 4-bromo-*N*-hydroxybenzimidoyl chloride (1.33 g, 5.6 mmol), were suspended in 20.0 mL of a 3:1 *t*-butanol/THF. Catalytic portion of CuI (76 mg, 0.4 mmol) was added, and the solution stirred for 10 min. After that KHCO<sub>3</sub> (0.565 g, 5.6 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. TLC analysis indicated complete consumption of starting materials. The yellow product was filtered off, and recrystallized from *n*-heptane. Gallardo, H.; Ely, F.; Bortoluzzi, A. J.; Conte, G. *Liq. Cryst.* **2005**, *32*, 667.
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18. *Crystal data of compound 14*: Formula C<sub>23</sub>H<sub>15</sub>NO, FW 321.36, monoclinic, space group *P*2<sub>1</sub>/*c*, cell parameters: *a* = 7.403(1) Å, *b* = 5.770(1) Å, *c* = 39.119(5) Å,  $\beta$  = 93.78(1)°, *V* = 1667.3(4) Å<sup>3</sup>, *Z* = 4,  $\rho_{\text{calc}}$  = 1.280 Mg/m<sup>3</sup>,  $\mu$  = 0.078 mm<sup>-1</sup>, *T* = 293 K, *F*(000) = 672, 2942 measured reflections, 2894 unique (*R*<sub>int</sub> = 0.0490), parameters 226, GOOF (*F*<sup>2</sup>) = 1.034, *R*<sub>1</sub> [*I* > 2 $\sigma$ (*I*)] = 0.0596, *wR*<sub>2</sub> (all data) = 0.1931. Crystallographic data (excluding structure factors) for the structure in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 703235. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).