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Expeditious preparation of isoxazoles from Δ^2-isoxazolines as advanced intermediates for functional materials

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The Letter is dedicated to Professor Hugo Gallardo on the occasion of his 60th birthday and his contribution for liquid crystals research in Brazil.

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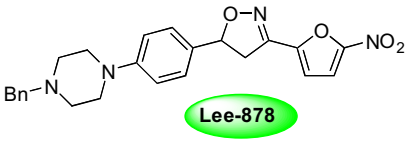
ABSTRACT

A collection of isoxazoles derivatives has been efficiently synthesized in three steps. The oximation reaction of aldehydes followed by nitrile oxide [3+2] 1,3-dipolar cycloaddition and MnO_2-oxidation reaction furnished the title compounds which were purified by simple filtration on celite®.

1. Introduction

Isoxazolines and isoxazoles are important 5-membered heterocycles widely spread out in many compounds with biological and technological properties. These related 'cousin' heterocycles are also present in a series of important compounds with well known medicinal properties. For instance, Lee-878, a nitrofuranyl isoxazoline is a potent inhibitor against *Mycobacterium tuberculosis*.[1] The outstanding in vitro activity of this compound led the Lee group to explore the isoxazolinic core as a privileged structure with anti-tuberculosis activity.[2,3]



Nucleosides and nucleotides chemistry are another example of the exploration of isoxazolines/isoxazole core as substitutes for the furanose ring in nucleoside analogues.[4] These structural modifications originated a new class of uracils tethered to isoxazolines[5] and isoxazoles[6], which showed potential antiviral and anticancer activity.

Isoxazolines and isoxazoles are substructures also present in many anti-inflammatory drugs, antibacterials,[7] in orally bioavailable factor Xa inhibitors,[8] and display in vitro antiprotozoal activities.[9] These small molecules act as activators of the cystic fibrosis transmembrane conductance regulator protein (CFTR), in the treatment of lethal genetic disease cystic fibrosis (CF). This disease is caused by mutations of the CFTR protein.[10] Beyond their broad spectra of biological activity, isoxazolines and isoxazoles are interesting intermediates in organic synthesis,[11] and play an important role in the synthesis of novel liquid-crystalline (LC) materials.[12]

From the synthetic point of view there are different approaches to prepare disubstituted isoxazoles. Condensation of 1,3-dicarbonyl compounds with hydroxylamine,[13] Michael addition of hydroxylamine hydrochloride to α,β-insaturated carbonyl compounds (chalcones) followed by cyclization,[14] nucleophilic addition of *N*-hydroxyl-4-toluenesulfonamide to α,β-unsatd. Aldehydes/ketones[15] are representative methods. Besides improvements, many procedures, have some inherent limitations such as low yields,

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co-products from side reactions, and both regioisomers are frequently isolated. Other strategies of preparation of regioisomeric isoxazoles in moderate yields are possible and involves the thermolysis of haloazidoalkenes and 2-halo-2*H*-azirines,[16] reaction of alkynes with ammonium cerium(IV) nitrate [$(NH_4)_2Ce(NO_3)_6$, CAN(IV)] in acetone,[17] diazotization of β-ketoesters followed by the addition of triethylamine and clorooxime.[18] More recently, Larock's group reported a three-step approach to synthesize isoxazoles involving an electrophilic cyclization of the ynone *O*-methyl oxime.[19]

The use of [3+2] 1,3-dipolar cycloaddition of nitrile oxides to alkynes constitutes an important alternative to prepare isoxazoles in solution or by combinatorial synthesis on solid support.[20] In fact, many nitrile oxides react with alkynes, with few exceptions,[21] leading often to a mixture of regioisomeric products, with low yields. To overcome this trouble Sharpless and co-workers reported that nitrile oxides react with alkynes at appreciable rates at room temperature in a highly selective manner and with good yields when copper(I) catalyst was added.[22] The performance of this procedure was also applied later in the synthesis of liquid crystals by Gallardo et al.[23] Although some alkynes are commercially available, the synthesis of mono-substituted alkynes can take two or more steps. In this sense, alkyne synthons can serve to alleviate the issues related on both alkyne preparation and cycloaddition regioselectivity.[24]

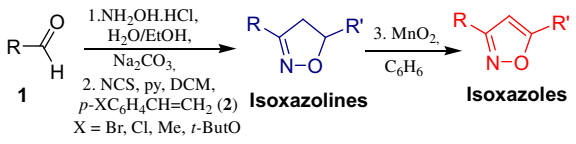
In our search for new LC molecules we have demonstrated the versatility of the [3+2] 1,3-dipolar cycloaddition as a suitable methodology to access a variety of 3,5-disubstituted isoxazoline liquid crystals.[25] Our previous results showed that the introduction of an isoxazoline ring flanked by aromatic rings or polar groups opened a route to prepare useful intermediates in the liquid crystals field, from themselves or their parent compounds isoxazoles. During the course of our investigation about isoxazolines, as a molecular kit for LC, we selected one of them and subjected it to a MnO_2-mediated oxidation process. We found that this reagent can easily oxidize 3,5-diarylisoxazoline to the corresponding 3,5-diarylisoxazole yielding LC materials with a large enantiotropic nematic mesophase.[26]

Herein we wish to report a facile and efficient synthesis of a collection of 3,5-disubstituted isoxazoles liquid crystals from isoxazolines, using the couple nitrile oxide [3+2] 1,3-dipolar cycloaddition/MnO_2-oxidation reactions.

In addition, halogenated variants of these core motifs open to us an avenue to be explored as starting materials for palladium-catalyzed reactions. So, the preparation of small molecular organic intermediate with potential technological applications, such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs) and liquid crystal displays (LCDs) can be achieved once it is an important task in the field of organic electronic materials-OEM.[27]

2. Results and discussion

Scheme 1 outlines the preparation of a general collection of isoxazolines and isoxazoles in a short and efficient sequence. Thus, aliphatic and aromatic aldehydes **1** were first converted into aldoximes by treatment with a hydroxylamine hydrochloride solution.



Scheme 1. Synthesis of isoxazoles from isoxazolines by [3+2] 1,3-dipolar cycloaddition followed by MnO_2-oxidation reaction.

The mixture was heated under reflux for 40 min, concentrated and left in the freezer overnight to give pure products as white solids. Next, using the [3+2] 1,3-dipolar cycloaddition reaction were prepared the key isoxazolines **3–13**, **25a–b**, and **26a–b** containing suitable groups for chemical transformations. These compounds were synthesized starting with the 1,3-dipolar component nitrile oxide, which was obtained in situ by reacting the aldoxime derivatives with NCS in pyridine[28], followed by the addition of a solution of different acceptors **2**, at room temperature for 4 h. The low yields observed in some examples are related with the low solubility of some oximes. The preparation of these isoxazolines derivatives provided us with an entry of a new class of precursors for high-performance liquid crystals materials.

With the valuable target intermediates 3,5-diarylisoxazolines synthesized, we focused our attention toward the transformation of them to isoxazoles through the oxidation protocol using activated γ−MnO_2 reagent.[29] The results are presented in Tables 1 and 2.

In order to determine the best reaction condition on the oxidation step, several other reagents were also tested[30] and the best results were obtained using activated MnO_2 oxidant in a Dean–Stark apparatus. By simple filtration and remotion of the solvent the final isoxazoles were synthesized in good to excellent yields.

All halogenated compounds synthesized are versatile building blocks that may be incorporated into low molar mass mesogenic structures for potential use on optical applications. The bromine atom at *para* position of the benzene ring offers the possibility to carry out a palladium-catalyzed cross-coupling reaction, which would lead to a very broad range of compounds with interesting properties in the field of organic materials.[31]

For example, compounds **23b** and **24b** could be valuable intermediates in the synthesis of bent core liquid crystals.[32] They are synthesized according to Scheme 2 where the delivery of free phenol **23b** is accomplished by the remotion of *t*-butyl group in AcOH/HBr medium. The alkylation of **23b** yields LC **23c**.

In order to extend the scope of our methodology, aliphatic aldoximes were also used as precursors for the nitrile oxides. The data collected in Table 3 show that the preparation of 3-alkyl-5-arylisoxazoline **25a–b** and **26a–b** and the corresponding isoxazoles 27a–**b** and **28a–b** is an attractive alternative to obtain advanced synthetic intermediates in the field of functional materials.

In fact, as can be seen from the results presented until now, the preparation of isoxazoles from isoxazolines constitutes of an alternative very efficient, fast, and clean method to reach useful intermediates in areas such as OEM and functional materials. Some

Table 1
Thermal data (°C) and yield (%) of the isoxazolines **3a–d**, **4–13**

Entry	X	Y	Yield (%)	Mp (°C)
3a	Br	OC_7H_{15}	53	119.8
3b	Br	OC_8H_{17}	75	115.8
3c	Br	OC_9H_{19}	54	113.3
3d	Br	$OC_{10}H_{21}$	52	111.8
4	Cl	OC_8H_{17}	43	109.5
5	Me	OC_8H_{17}	30	94.8
6	Br	Br	34	123.2
7	Cl	Br	14	120.0
8	Me	Br	93	142.5
9	Br	NO_2	42	132.0
10	Cl	NO_2	19	140.5
11	Me	NO_2	14	122.0
12	^{t}ButO	Br	57	122.0
13	^{t}ButO	NO_2	20	143.0

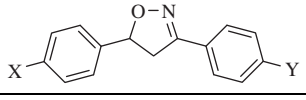
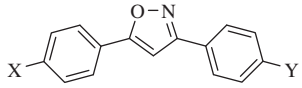
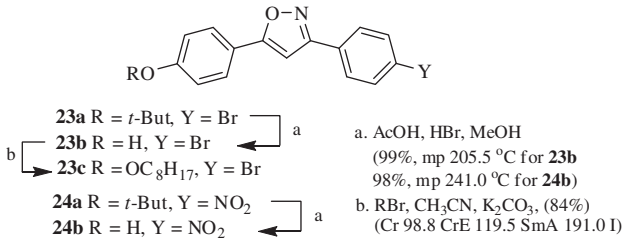


Table 2
Transition temperatures[a] (°C) and yield (%) of the isoxazoles **14a–d**, **15–24b**

Entry	X	Y	Yield (%)	Physical appearance
14a	Br	OC_7H_{15}	99	Cr 109.3 CrE 128.0 SmA 191.3 I
14b	Br	OC_8H_{17}	98	Cr 93.0 CrE 129.0 SmA 191.0 I
14c	Br	OC_9H_{19}	50	Cr 108.6 CrE 126.0 SmA 184.5 I
14d	Br	$OC_{10}H_{21}$	97	Cr 99.0 CrE 128.0 SmA 186.0 I
15	Cl	OC_8H_{17}	70	Cr 115.5 CrA 180.0 N 184.0 I
16	Me	OC_8H_{17}	90	Cr 105.9 N 132.2 I
17	Br	Br	94	Cr 214.4 I
18	Cl	Br	47	Cr 200.0 I
19	Me	Br	67	Cr 210.0 I
20	Br	NO_2	62	Cr 224.8 I
21	Cl	NO_2	66	Cr 222.2 I
22	Me	NO_2	70	Cr 182.5 I
23a	*t*-ButO	Br	95	Cr 157.8 I
24a	*t*-ButO	NO_2	95	Cr 181.0 I



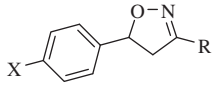
[a] Data obtained by polarizing optical microscopy, POM; Cr = crystal phase; CrE = Crystal E phase; SmA = Smectic A phase and I = Isotropic phase.



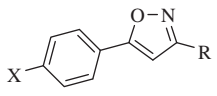
Scheme 2. Preparation of phenols **23b** and **24b** by deprotection reaction of **23a** and **24a** and the corresponding alkylated **23c**.

Table 3
Thermal data (°C) and yield (%) of the isoxazolines **25a**,**b**–**26a**,**b** and isoxazoles **27a**,**b**–**28a**,**b**, respectively

Entry	R	X	Yield (%)	Mp (°C)
25a	C_4H_9	Br	25	[a]
25b	C_4H_9	Me	44	[a]
26a	C_7H_{15}	Br	87	[a]
26b	C_7H_{15}	Me	49	[a]

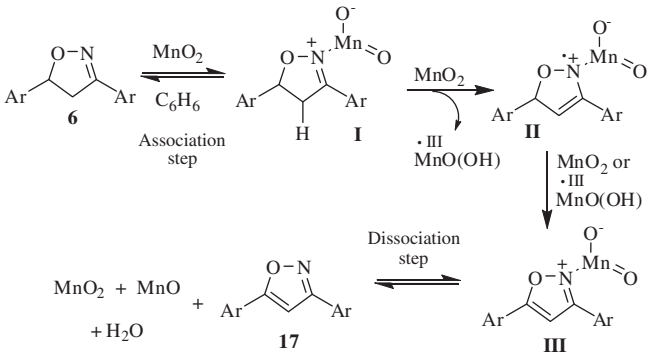


27a	C_4H_9	Br	48	48.3
27b	C_4H_9	Me	89	a
28a	C_7H_{15}	Br	70	76.0
28b	C_7H_{15}	Me	72	55.5



[a] Viscous liquid at room temperature.

of them **14a–d**, **15**, **16,** and **23c** are liquid crystals itself. The crystal E phase founded in these compounds makes them very promising candidates for their application in the field of OFETs. It is interesting to see that exchanging the terminal groups in **14a–d** to **23c** does not modify the nature of the mesophase. We anticipated that the optical texture of the liquid crystalline A phase of compound **14a**, viewed between crossed polarisers (see SI) on cooling, is transferred to the smectic E phase, and then to the crystalline state. This paramorphosis phenomenon is important to control the short-range spatial order present in the smectic phases on cooling.[33]



Scheme 3. Stepwise reaction sequence for the manganese dioxide oxidation of isoxazoline **6**.

Also, the nature of mesophase is dependent on the terminal group attached in the *para* position of benzene ring if we compare **14d**, **15,** and **16**.[34] As expected all isoxazolines in Tables 1 and 3 are not liquid crystals considering that they are not completely conjugate and planar.

The 3-alkyl-5-arylisoxazoles **27a–b** and **28a–b** are other precursors for obtaining new low molar mass liquid crystal.[35] These new precursors have the benzene ring substituted by short and medium alkyl chain at C-3 position of the isoxazole ring. The properties could be tailored by changing the molecular shape. A detailed synthetic study of preparation of the new compounds from these isoxazoles is now in progress and will be reported soon.

The mechanistic proposal for the formation of 3,5-disubstituted isoxazoles from 3,5-disubstuted isoxazolines with activated manganese dioxide is shown in Scheme 3. The mechanism of oxidation of benzyl alcohol with manganese dioxide has been studied by Goldman.[36] According to his studies, the rate-determining step in the oxidation of benzyl alcohols with activated manganese dioxide involves the cleavage of the α-CH bond, and that the assumed adsorption step is reversible. More recently, Srivastava et al. reported the conversion of 4,5-dihydro-1,2,4-oxadiazoles to 1,2,4-oxadiazoles by an oxidation process mediated by MnO_2 and NaOCl reagents.[37] The mechanism of this transformation was discussed by the authors. Similar mechanism should be considered for the oxidation of 3,5-disubstituted isoxazolines to 3,5-disubstituted isoxazoles as exemplified by **6** to **17** (Scheme 3). Initially, **6** interacts reversibly at the surface of manganese dioxide via coordination between N and MnO_2 forming the complex **I** (to activate the Hα-iminic hydrogen), which undergoes oxidation via hydrogen-atom transfer from **I** to another equivalent of MnO_2 to form the stable radical **II**. Abstraction of a hydrogen radical from C-3 generates **III**, which then is dissociated delivering the isoxazole **17** and the inorganic species (MnO_2, MnO, and H_2O).

In summary, we have synthesized a collection of isoxazoles which are rapidly accessed by two efficient methodologies—the nitrile oxide [3+2] 1,3-dipolar cycloaddition followed by MnO_2-oxidation reaction. The final isoxazoles are valuable building blocks which may be transformed into potential materials in OEM or functional materials.

3. Experimental section

3.1. Synthesis

4-*n*-Alkyloxybenzadehyde and the corresponding oximes were prepared according to Refs. 25,26. The general procedure for the preparation of 3,5-disubstituted isoxazolines is described as follows: To a solution of alkene (4.25 mmol) in CH_2Cl_2 (10 ml), at 0 °C and under inert atmosphere, were added NCS (4.67 mmol)

and pyridine (6.37 mmol). A solution of aldehyde oxime (4.25 mmol) in CH_2Cl_2 (12 ml) was added dropwise and stirred for 4 h at room temperature. The mixture was washed with HCl 1 M (3 × 20 ml), brine, (2 × 20 ml) and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 afforded the crude product, which was recrystallized from ethanol to give the pure product as a white solid or isolated by column chromatography using a mixture of EtOAc/hexane (1:9).

General procedure for the oxidation reaction. To a flask adapted with a Dean-Stark were added 3,5-disubstituted isoxazoline (1.2 mmol), benzene (25 ml), and γ-MnO_2 (6 mmol). The mixture was heated under reflux for 10 hours. After that, it was filtered over celite and concentrated in vacuum to give a pale white solid which was purified by recrystallization in ethanol. Data for **14a**. Yield: 99%; mp 109.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2H, J = 8.4 Hz, Ar), 7.68 (d, 2H, J = 8.7 Hz, Ar), 7.60 (d, 2H, J = 8.4 Hz, Ar), 6.97 (d, 2H, J = 8.4 Hz, Ar), 6.76 (s, 1H), 4.00 (t, 2H, J = 6.4 Hz, OCH_2CH_2), 1.81 (m, 2H, OCH_2CH_2), 1.5–1.3 (m, 8H, $(CH_2)_4$), 0.90 (t, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR (75.5 Hz, $CDCl_3$) δ 169.0, 162.7, 160.7, 132.2, 128.1, 127.3, 127.2, 126.4, 124.4, 121.1, 114.8, 97.6, 68.1, 31.8, 29.2, 29.0, 26.0, 22.6; Elem. Anal. Calcd for $C_{22}H_{24}NO_2Br$: C, 63.77; H, 5.84; N, 3.38. Found: C, 63.63; H, 5.63; N, 3.42.

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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.2011.09.122.

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