Tetrahedron Letters 55 (2014) 1557–1560

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles and their behavior of liquid crystallines

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ARTICLE INFO

Article history:
Received 21 October 2013
Revised 8 January 2014
Accepted 16 January 2014
Available online 23 January 2014

Keywords:
3,5-Disubstituted 1,2,4-oxadiazoles
Liquid crystal
Nematic phase
Phase transition
Smectic phase

ABSTRACT

The synthesis of 3,5-disubstituted 1,2,4-oxadiazoles by the cyclocondensation of amidoximes with trifluoroacetic anhydride or benzoic acid derivatives in moderate to high yields is described. The study on the phase transition behavior has disclosed that some of the synthesized oxadiazoles show smectic or nematic phases depending on their structures, which have the high potential application as liquid crystalline monomers.

3,5-Disubstituted 1,2,4-oxadiazoles are important five-membered heterocyclic compounds not only occurring in natural and artificial products showing interesting biological and physiological activities,[1] but also being applied as the functionalized organic materials, particularly as liquid crystalline monomers.[1a] It has been found that the high polarization of the electronic system in heterocyclic moieties can easily adjust the phase transition temperature and change the types of liquid crystal phase by controlling the polarity and configuration of molecules,[2] also may result in the increase of molecular dipole and dielectric anisotropy.[3] Therefore, as one of the typical five-membered heterocycles, recently a variety of 3,5-diaryl-1,2,4-oxadiazole derivatives have been synthesized, and applied as the bent-core liquid crystals with intriguing properties.[4]

There is no doubt that the development of the excellent liquid crystal displays (LCDs) with the advantages of fast response, high contrast ratio, and low driving voltage greatly depends on the design and synthesis of new types of liquid crystalline monomers and liquid crystal mixtures. It can be expected that heterocyclic compounds having the strong electron withdrawing group of trifluoromethyl as a substituent should lead to the further increase of molecular dipole and dielectric anisotropy, this Letter therefore describes the synthesis of 3-aryl-5-trifluoromethyl (**2a**–**i**) and 3,5-diaryl 1,2,4-oxadiazole derivatives (**2j**–**k**), as well as the investigation on their phase transition behavior.

There have been many synthetic routes for the formation of 3,5-disubstituted 1,2,4-oxadiazoles,[5] but one of the most efficient methods is the cyclization of *O*-acylamidoximes, which can be formed from the acylation of amidoximes with acid anhydride or carboxylic acid derivatives.[6] Therefore the reaction of easily available amidoximes with trifluoroacetic anhydride (TFAA) under the modified reaction conditions (without the use of base) was employed for the synthesis of 3-aryl-5-trifluoromethyl-1,2,4-oxadiazoles, and the obtained results are included in Table 1. The choice of the structural species of the R group (aryl group) in the present study such as fluorinated aryl, cyclohexyl aryl, is based on the known knowledge on their application as the fundamental structural moieties in liquid crystallines. As shown in Table 1, a variety of 5-trifluoromethyl-1,2,4-oxadiazoles bearing different aryl groups at 3-position could be synthesized in good yields in toluene under refluxing conditions for 4 h, and the structures of all the target products were confirmed by their ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and elemental analyses or HRMS.[7]

The proposed mechanism for the formation of 3-aryl-5-trifluoromethyl-1,2,4-oxadiazoles is shown in Scheme 1, which involves the formation of *O*-trifluoroacetyl amidoxime as the crucial intermediate, and followed by cyclization reaction via nucleophilic addition and dehydration.

In addition, the synthesis of 3,5-diaryl-1,2,4-oxadiazole derivatives was also studied by the first direct cyclocondensation of amidoxime with benzoic acid derivatives via the formation of the corresponding amides as the intermediates with the use of *N*-ethyl-*N*′-dimethylaminopropylcarbodiimide hydrochloride

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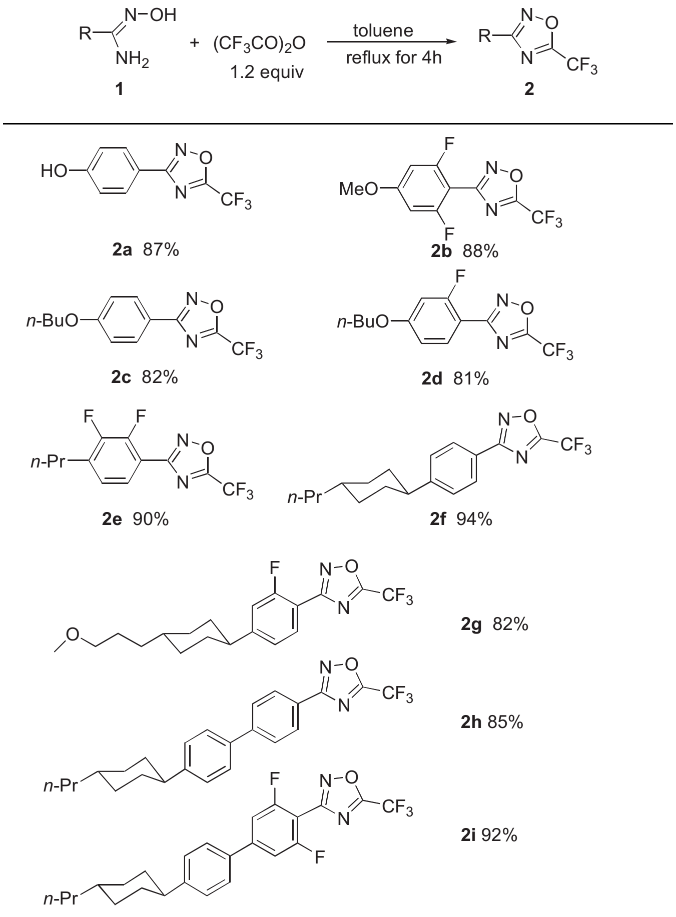
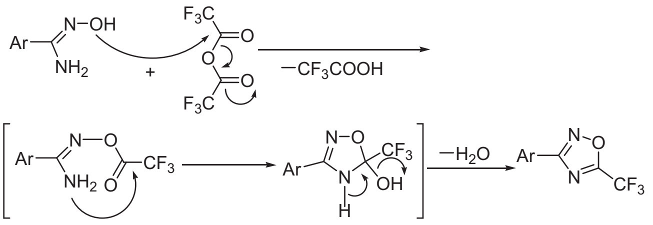
0040-4039/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2014.01.066

Table 1

Synthesis of 5-trifluoromethyl 1,2,4-oxadiazoles[a]



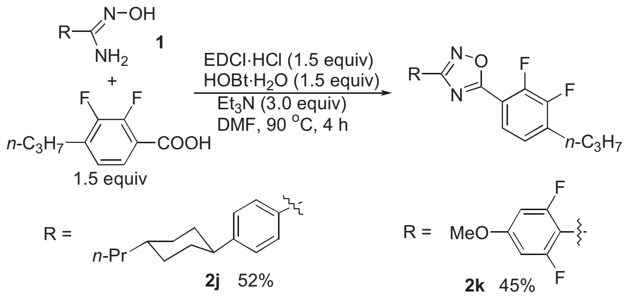
[a] The reactions were carried out with 2.0 mmol of **1** and 2.4 mmol of trifluoroacetic anhydride in 30.0 mL of toluene under reflux for 4 h.



Scheme 1. Plausible mechanism for the formation of 1,2,4-oxadiazoles.

(EDCI·HCl) and 1-hydroxybenzotriazole hydrate (HOBt·H_2O) as the condensing agents. As shown in Scheme 2, **2j** and **2k** could be synthesized in 52% and 45% yields, respectively. The obtained results indicate that EDCI·HCl and HOBt H_2O are the efficient condensing agents for the selective condensation of amidoxime with acids to give amides,[8] which was further transferred to the desired 3,5-diaryl-1,2,4-oxadiazoles under the same conditions. Therefore, the presented procedure has developed a new and alternative route for the construction of the 1,2,4-oxadiazole ring.

The phase transition behavior of the solid products was investigated by differential scanning calorimetry (DSC) and polarizing optical microscopy (POM) to study their thermal properties of the melting points (mp) and/or phase transition temperatures (Table 2), as well as textures of phase (Fig. 1). It was found that the mp and phase transition temperature greatly depend upon the molecular and electronic structures of oxadiazoles. As shown in Table 2, **2c** and **2f** show smectic phases, **2h**, **2i**, and **2j** show



Scheme 2. Synthesis of 3,5-diaryl-1,2,4-oxadiazoles from the condensation of amidoximes with benzoic acid derivatives.

Table 2

Melting points (°C) or phase transition temperatures (ptt, °C) of 3,5-disubstituted 1,2,4-oxadiazoles by DSC

Oxadiazole	mp	ptt	Oxadiazole	mp	ptt
2a	74.4–75.2		**2h**		Cr 114.7 S 184.4 N 258.1 I
2c		Cr 48.5 S 85.2 I	**2i**	69.8–69.9	141.6 N 173.2 I
2f		Cr 83.4 S 96.8 I	**2j**		Cr 71.7 N 153.5 I
2g	41.6–42.2		**2k**	89.8–90.4	

nematic phases with a wide nematic temperature range from 184.4 to 253.1 °C, 141.6 to 173.2 °C, and 71.7 to 153.5 °C, respectively. It should be noted that **2h–j** possess a common structural moiety of *n*-propyl–cyclohexyl–phenyl at 3-position of the oxadiazole ring, which is a possible crucial structure to show the nematic phase. Since **2h–j** have the wide nematic temperature range, they have highly potential application in the preparation of practical liquid crystal mixture for LCDs as the liquid crystalline monomers. The typical schlieren textures of **2c**, **2f**, **2h**, **2i**, and **2j** are shown in Figure 1.

In addition, as shown in Table 1 **2h** and **2i** have the same core structure, but they show considerable different phase transition temperature and nematic temperature range. On the basis of the DFT calculations (Fig. 2), it has been found that both **2h** and **2i** have the similar configurations with the 3-aryl group (**2h**), or 3-fluoroaryl group (**2i**) and the oxadiazole ring being in the same plane. These results indicate that the introduction of *ortho*-fluorines in the aryl group of 3-position of the oxadiazole ring cannot affect the configuration of the substituted oxadiazole ring, but is the crucial factor to greatly change the phase transition behavior. Furthermore, as shown in Figure 2, the configuration of 3,5-diary groups and oxadiazole ring in **2j** is also in the same plane. All these observed results are very interesting and important to provide a hint to elucidate the relationship of structure or configuration with phase transition behavior.

In conclusion, we have synthesized a number of 3-aryl-5-trifluoromethyl- and 3,5-diaryl-1,2,4-oxadiazole derivatives in moderate to high yields by the cyclocondensation of amidoximes with either trifluoroacetic anhydride or benzoic acids. It is the first Letter on the formation of 3,5-diaryl-1,2,4-oxadiazoles by direct cyclocondensation of amidoxime with benzoic acids in the presence of EDCI·HCl and HOBt·H_2O as the condensing agents, providing a new and alternative route for the construction of the 1,2,4-oxadiazole ring. The investigation on the phase transition behavior of the synthesized 1,2,4-oxadiazole disclosed that the molecular and electronic structures greatly affect their thermal properties of mp and cp, **2c** and **2f** show smectic phases, and **2h–j** show nematic phases with a wide nematic temperature.

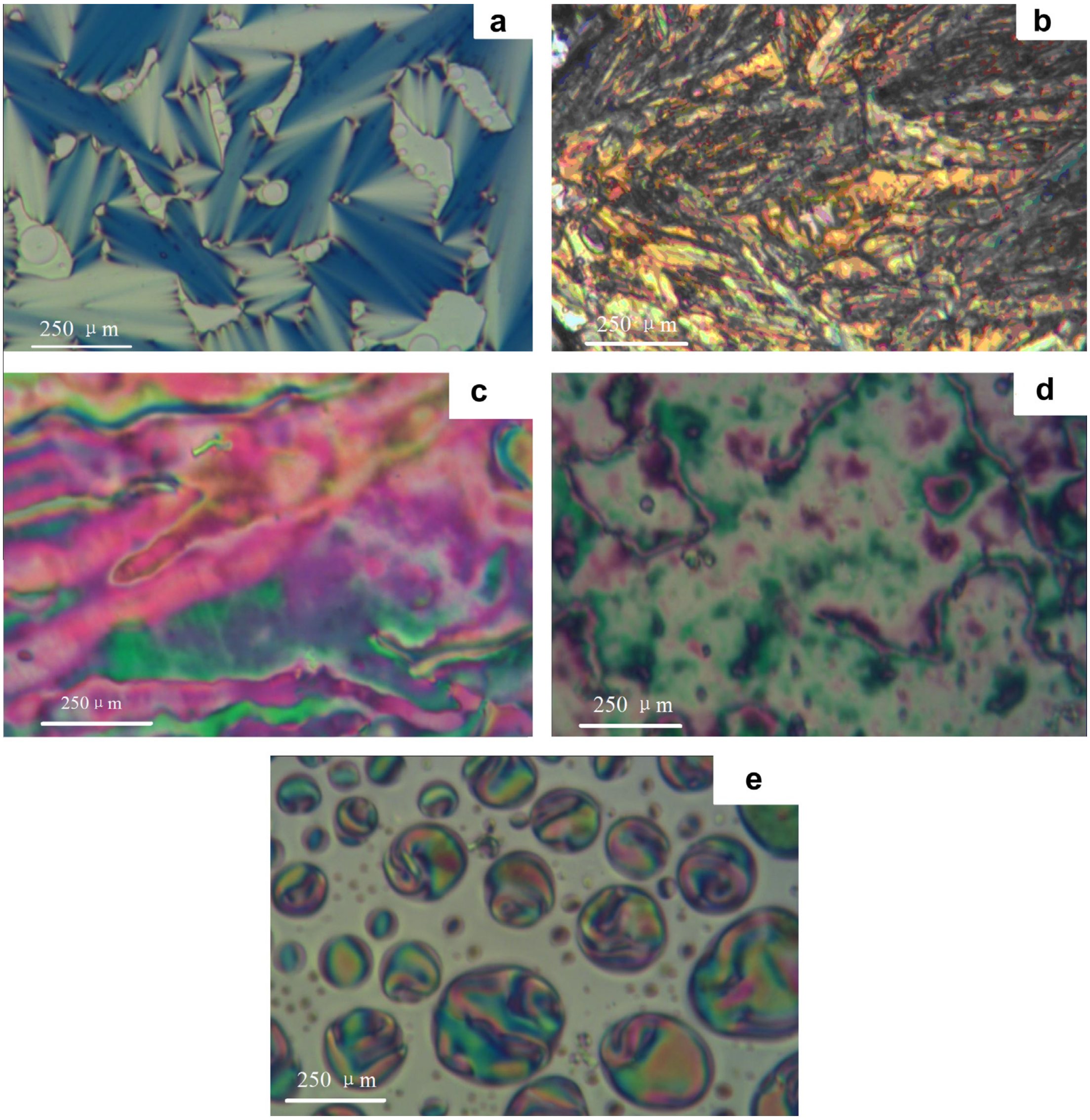


Figure 1. (a) Smectic texture of **2c** at 50.2 °C during cooling. (b) Smectic texture of **2f** at 85.1 °C during cooling. (c) Schlieren texture of the nematic phase of **2h** at 235.4 °C during cooling. (d) Schlieren texture of the nematic phase of **2i** at 150 °C during cooling. (e) Schlieren texture near the I–N transition of **2j** at 153.4 °C during cooling.

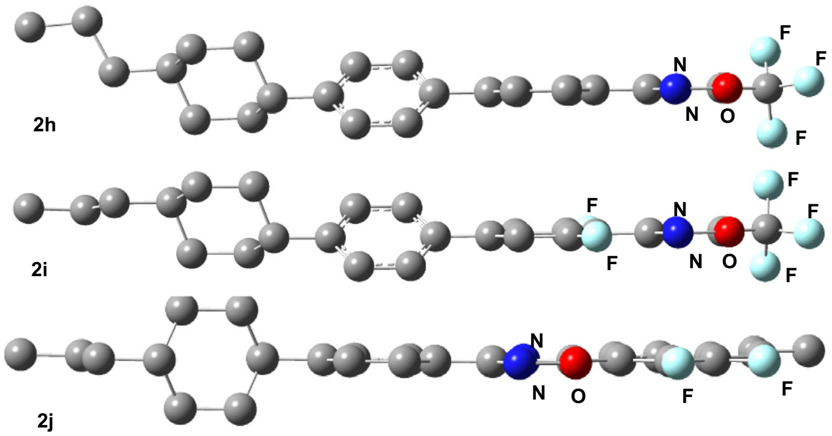


Figure 2. The configuration of **2h**, **2i**, and **2j** by DFT calculations using Gaussian 09. (Hydrogen atoms are omitted for clarity.)

Work is in progress to apply **2h**–**j** as the liquid crystalline monomers in the making practical liquid crystal mixture for LCDs.

The general experimental procedure for the synthesis of 3-aryl-5-trifluoromethyl 1,2,4-oxadiaozles (**2a**–**i**): a mixture of amidoximes (2.0 mmol) and trifluoroacetic anhydride (504.0 mg, 2.4 mmol) in dried toluene (30 mL) was refluxed for 4 h. After removal of the volatiles, the residue was treated with brine (30 mL), and then extracted with EtOAc (3 × 20 mL). The combined organic layers were then dried over Na_2SO_4 and evaporated. **2a**–**i** was purified by chromatography (petroleum ether).

*The general experimental procedure for the synthesis of 3,5-diaryl-1,2,4-oxadiazole derivatives (**2j**–**k**):* A mixture of amidoximes (4.0 mmol), 2,3-difluoro-4-*n*-propylbenzoic acid (1.2 g, 6.0 mmol), EDCI·HCl (1.2 g, 6.2 mmol), HOBt·H_2O (811.0 mg, 6.0 mmol), and triethylamine (1.7 mL, 12.0 mmol) in dried DMF was heated to 90 °C for 4 h with stirring. The mixture was then extracted with EtOAc (3 × 20 mL), and the combined layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to a yellow residue. **2j**–**k** was purified by chromatography (petroleum ether).

Acknowledgment

This project was supported by the National Natural Science Foundation of China (21032004).

Supplementary data

Supplementary data (general method, characterization data and charts of ^1H, ^{13}C, and ^{19}F NMR for all products are concluded) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.066.

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