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## Liquid Crystals

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# Preliminary communication 

# Applying click chemistry to synthesis of chiral [1,2,3]-triazole liquid crystals 

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1,3-Dipolar cycloaddition of organic azides to triple bonds, or 'click chemistry' has been used in order to obtain chiral 1,4-disubstituted [1,2,3]-triazoles. Liquid crystalline compounds bearing such heterocycles were prepared and $\operatorname{SmA}$ and $\mathrm{N}^{*}$ (cholesteric) phases identified. Contact experiments indicated a right-handed helix (RH-helix) for the cholesteric phase, and attempts to corroborate experimental and theoretical results are presented.
[1,2,3]-Triazoles are $N$-heterocyclic compounds, not present in natural products, which display high biological activity including anti-HIV [1], $\beta$-lactamase inhibitory [2] and antiepileptic activities [3]. In addition, members of this class have found application in materials chemistry as dyes, corrosion inhibitors, photostabilizers and photographic materials [4]. However, to the best of our knowledge there are no reports of the use of this five-membered ring in liquid crystals, and only a few examples containing the regioisomeric [1,2,4]-triazole [5]. A number of different methods have been developed for the synthesis of [1,2,3]-triazoles, such as intramolecular cyclization of bishydrazones or diazointermediates, miscellaneous oxidations and three-component coupling (TCC) [6]. But the most successful method seems to be 1,3-dipolar cycloadditions of organic azides to triple bonds, also known as 'click chemistry'. If the cycloaddition is thermally induced a $1: 1$ mixture of the 1,4 and $1,5-$ regioisomers is usually obtained [7]. In order to improve the 1,4 -regioselectivity, reactions are carried out catalytically using $\mathrm{Cu}(\mathrm{I})$ or $\mathrm{Cu}(\mathrm{II})$ salts and sodium ascorbate [8], using water as solvent [9] or in encapsulated systems [10].

We are interested in chiral liquid crystals containing the heterocycle [1,2,3]-triazole in special materials presenting cholesteric $\left(\mathrm{N}^{*}\right)$ and ferroelectric $\left(\mathrm{SmC}^{*}\right)$ mesophases. In these phases molecules form helical macrostructures with a specific handedness (righthanded, P , or left-handed, M ) reflecting configurational, conformational and phase chiralities [11]. Such

[^0]self-assembled systems also provide interesting models for the study of helical structures of living systems such as proteins, DNA and collagen [12].

Scheme 1 illustrates the synthesis of key intermediates used to prepare the target mesogens. Aliphatic and aromatic azides 2 and $\mathbf{3}$ were prepared by nucleophylic displacement from mesylate 1 and the diazonium salt of $4-n$-decyloxyaniline, respectively.


i. $1, \mathrm{~K}_{2} \mathrm{CO}_{3}, 90 \%$
ii. 2-methyl-3-butyn-2-ol,

i. $\mathrm{BnBr}, \mathrm{K}_{2} \mathrm{CO}_{3}, 79 \%$
ii. 2-methyl-3-butyn-2-ol,TEA,
TPP, $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}, \mathrm{CuI}, 65 \%$
$\downarrow$ iii. NaOH , toluene, $62 \%$


Scheme 1. Synthesis of key intermediates.

Triple bonds were constructed starting from 4-bromophenol by copper-palladium catalysed crosscoupling (Sonogashira-Tohda-Hagihara coupling) [13] with mebynol (2-methyl-3-butyn-2-ol) and subsequent deprotection. To obtain the desired 1,4-disubstituted [1,2,3]-trizoles $\mathbf{6}$ and $\mathbf{1 0}$ (schemes 1 and 2), three reaction systems were selected, with the results displayed in the table. Water was used as solvent (method A) [9] or co-solvent (methods B [8 a] and C). The addition of water, besides having economic and environmental advantages, led to improvements in the rate of 1,3-cycloadditions and regioselectivity.


Scheme 2. Preparation of the mesogenic targets and their transition temperatures, $\mathrm{Cr}=$ crystal; $\mathrm{N}^{*}=$ chiral nematic (cholesteric); $\mathrm{SmA}=$ smectic A and $\mathrm{I}=$ isotropic liquid. Data obtained from optical microscopy and DSC measurements. Values in parentheses indicate heat of the transition ( $\mathrm{kJ} \mathrm{mol}^{-1}$ ).

Table. 1,3-Dipolar cycloaddition results. ${ }^{\text {a,b }}$

| Entry | Reagents | Method | Triazole yield/\% | Alkyne <br> recov./\% |
| :--- | :---: | :---: | :---: | :---: |
| 1 | $\mathbf{2 + 5}$ | A | - | 100 |
| 2 | $\mathbf{2 + 5}$ | B | - | 100 |
| 3 | $\mathbf{2 + 5}$ | C | 64 | 11 |
| 4 | $\mathbf{3 + 4}$ | A | $63^{\text {c }}$ | 25 |
| 5 | $\mathbf{3 + 4}$ | B | 35 | 48 |
| 6 | $\mathbf{3 + 4}$ | C | 90 | 7 |

[^1]Apparently, this occurs because there is an alteration of the FMOs energies, indicating a predominance of the dipole-HOMO and dipolarophile-LUMO interactions [14]. From methods B and C only one product was obtained out of two possible regioisomers, namely the 1,4-disubstituted [1,2,3]-triazole. No procedure gave total conversion. Best results were achieved using method C developed by us, which consists of a modification of the original solid phase method of Meldal and collaborators [15].

In a typical experimental procedure C (entry 3, the table) the chiral alkyne $4(0.216 \mathrm{~g}, 1.15 \mathrm{mmol})$, CuI $(0.021 \mathrm{~g}, 0.115 \mathrm{mmol})$ and TEA $(0.02 \mathrm{ml}, 0.115 \mathrm{mmol})$ were suspended in $1 / 1$ ethanol/water $(10 \mathrm{ml})$. To the heterogeneous and vigorously stirred mixture the azide 3 ( $0.315 \mathrm{~g}, 1.15 \mathrm{mmol}$ ) was added dropwise. Gentle reflux $\left(60^{\circ} \mathrm{C}\right)$ was maintained for 48 h . Water $(20 \mathrm{ml})$ was added and the flask cooled in crushed ice. The precipitate was collected by filtration and washed with water. Recrystallization from hexane gave $0.478 \mathrm{~g}(90 \%)$ of $\mathbf{1 0}$ as a white powder. Mother liquor was concentrated furnishing $0.040 \mathrm{~g}(7 \%)$ of the starting alkyne 4.

Structural characterization was carried out by NMR based on the strong NOE effect observed between the proton of the triazole ring and the methyl group from the chiral chain, suggesting that the triazole proton and methyl group are in close proximity as in the $1,4-$ disubstituted compound. Figure 1 shows a partial 2D NOESY of 6. After hydrogenolysis of the benzyl group it was possible to obtain a single crystal of 7 and its structure was determined by X-ray crystallography (figure 2), which confirmed the 1,4-disubstitution. ${ }^{\dagger}$

In consideration of our interest in cholesteric ( $\mathrm{N}^{*}$ ) and ferroelectric ( $\mathrm{SmC}^{*}$ ) phases, targets were designed incorporating units into the mesogenic core that potentially confer such properties, namely phenylisoxazole [16] and 1,4-biphenyl-[1,2,3]-triazole (isogeometric to 2,5-biphenyl-[1,3,4]-thiadiazole) [17].

Compounds $\mathbf{9}$ and 10 displayed the liquid crystalline chiral nematic and smectic A phases, but ferroelectric behaviour was not observed. We believe the bend imposed by the [1,2,3]-triazole ring is so large that the effective polar packing necessary to build up a $\mathrm{SmC}^{*}$ is disrupted. The mesomorphic properties of compounds 9 and 10 were identified by plane-polarized light

[^2]

Figure 1. Partial 2D NOESY spectrum of 6. The NOE assigned by an arrow confirms the 1,4 -substitution product shown as an AM1 minimized structure.


Figure 2. ORTEP diagram of compound 7.
microscopy and differential scanning calorimetry (DSC). Mesomorphic textures are presented in figure 3.

SmA phases, when consisting of chiral molecules, can adopt a helical ordering thus forming a frustrated structure called twist grain boundary $A$ (TGBA) [18]. However, all textures observed by polarizing optical microscopy for $\mathbf{1 0}$ are orthogonal SmA , typical where the molecules are arranged in layers so that their long axes are on average perpendicular to the diffuse layer planes. Figure $3(b)$ illustrates a contact preparation used to establish the helical twist direction for the $\mathrm{N}^{*}$ phase of 9 . The contact studies were carried out on an Olympus BX50 polarizing microscope in conjunction with a Mettler Toledo FP-90 heating stage and an


Figure 3. Photomicrographs of (a) the focal-conic fan texture of the SmA phase of compound 10 at $147.1^{\circ} \mathrm{C}(66 \times)$, and (b) contact preparation between 9 (right) and the laevo standard $\mathrm{N}^{*}$ material cholesteryl benzoate (left) at $162.0^{\circ} \mathrm{C}(33 \times)$. The contact region (middle) shows a continuous change in pitch without diverging, indicating the same twist direction.

Exposure control unit PM-30. Cells of $10 \mu \mathrm{~m}$ thickness were purchased from Linkam Scientific Instruments Ltd and the experiment conducted as described by Goodby et al. [19]. For $\mathrm{N}^{*}$ an empirical relation was established between the helical ordering of the phase and the chirality in the flexible chain [20]. According to the Sol-Rel, Sed-Rod rules, helical twist direction and


Blue: Triazole as part of the core: Sed $\longrightarrow$ (d)-LH-helix Green: Triazole as part of the chain: Sed $\longrightarrow$ (d)-LH-helix Brown: Triazole as part of the chain: Sol $\longrightarrow$ (I)-RH-helix

Figure 4. Estimation of the helical twist direction of the $\mathrm{N}^{*}$ phase of 9 using the Gray-McDonnell rules.
the rotation direction of plane polarized light depend strongly on the absolute spatial configuration of the chiral centre ( $R$ or $S$ ) and the distance separating the chiral centre from the rigid core (odd or even number of atoms). Contact studies for the $\mathrm{N}^{*}$ phase of 9 indicate a laevo-rotation that corresponds, by definition, to a right handed-helix (RH-helix). Figure 4 shows an attempt to verify an agreement between experimental results and the Gray-McDonnell empirical rules.

The greatest difficult consists of determining the parity (odd or even), in other words where to start the count, by virtue of the presence of the triazole heterocycle. In the initial rules for cholesterics the numbering should run from the last phenyl ring to the asymmetric centre. However, when conjugated spacer groups (e.g. carboxyl) are involved a little confusion can arise because in this situation the linking groups may be considered as part of the rigid core. In order to avoid this Goodby et al. [19] suggested the count should begin from the last bond of the core, which is approximately coaxial to the long axis of the core. Taking all of this into account, figure 4 indicates the three possibilities for establishing the odd-even parity. The labelling in blue considers the [1,2,3]-triazole ring as part of the core and the other two in green and brown consider it as part of the chiral chain (first bond coaxial to the core). Of those options only the brown numbering is able to reproduce the experimental results-(1)-RH-helix. But even though the count is correct, factors other than configurational ( $R$ or $S$ ) chirality and distance of the chiral centre from the core may influence the helical macrostructure formation. Although such guidelines work well in predicting the helical twist direction in a simple $\mathrm{N}^{*}$ phase without electron-withdrawing groups at the chiral the centre [21], in $\mathrm{SmC}^{*}$ [19] materials (with some modifications) and in optically active poly(3,4-diakoxythiophenes) [22], they fail to explain the pitch inversion observed in some cholesteric mesogens, and chirality on a large scale [23]. It has been suggested that dipolar interactions, conformational interconversion and packing schemes play an important role in determining phase and object handedness [24].

In summary, we have prepared for the first time chiral LC compounds containing the [1,2,3]-triazole ring, using as a crucial step the Huisgen $\mathrm{Cu}(\mathrm{I})$-catalysed cycloaddition. The results are very promising and design and the synthesis of related mesomorphic optically active [1,2,3]-triazoles is in progress and will be reported in due course.

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-262000. Copies of the data can be
obtained from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

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[^1]:    ${ }^{\text {a }}$ Method A: 1 eq. azide : 1 eq. alkyne in water at $85^{\circ} \mathrm{C}$. Method B: 1 eq. azide : 1 eq. alkyne : $1 \mathrm{~mol} \% \mathrm{CuSO}_{4} \cdot 5 \mathrm{H}_{2} \mathrm{O}: 5 \mathrm{~mol} \%$ sodium ascorbate in $1 / 1 \mathrm{H}_{2} \mathrm{O} / \mathrm{Bu}^{t} \mathrm{OH}$ at rt . Method C : 1 eq . azide : 1 eq. alkyne : $10 \mathrm{~mol} \% \mathrm{CuI}: 10 \mathrm{~mol} \%$ TEA in $1 / 1 \mathrm{H}_{2} \mathrm{O} /$ EtOH at $60^{\circ} \mathrm{C}$. ${ }^{\mathrm{b}}$ Isolated yields after 48 h . Prolonged reaction times were not beneficial. ${ }^{\text {c }} \mathrm{A} 1 / 1$ mixture of $1,4-$ and $1,5-$ triazole regioisomers was obtained.

[^2]:    ${ }^{\dagger}$ Formula: $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}, \quad M W=231.30, T=293 \mathrm{~K}$, colourless crystal, crystal size $0.43 \times 0.33 \times 0.30 \mathrm{~mm}^{3}$, orthorhombic, space group $P 2_{1} 2_{1} 2_{1}, a=7.928(1), b=12.633(2), c=$ 13.104(4) $\AA, \quad V=1312.4(5) \AA^{3}, \quad Z=4, \quad \rho_{\text {calc }}=1.171 \mathrm{~g} \mathrm{~cm}^{-3}$, $\mu\left(\mathrm{Mo}-\mathrm{K}_{\alpha}\right)=0.077 \mathrm{~mm}^{-1}, F(000)=496,1814$ unique, 155 parameters, $\operatorname{GOOF}\left(F^{2}\right)=1.016$, final indices $R_{1}$ $[I>2 \sigma(I)]=0.0468,{ }_{\mathrm{w}} R_{2}($ all data $)=0.1179$.

