Tetrahedron Letters 45 (2004) 7591–7594

Tetrahedron Letters

Development of a new traceless aniline linker for combinatorial solid-phase parallel synthesis of rod-shaped liquid crystals with an azomethine linkage

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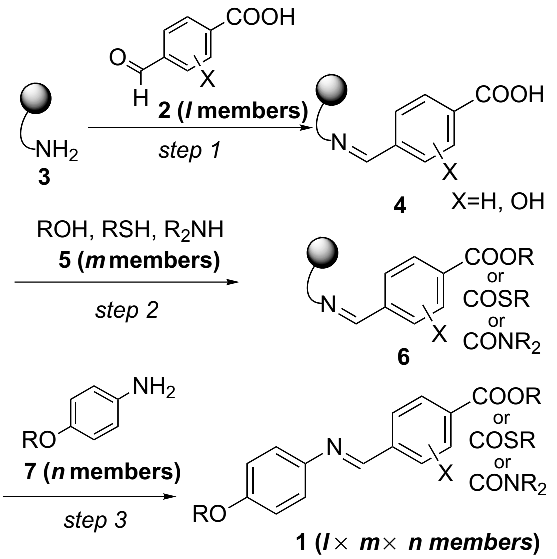
Received 28 July 2004; revised 16 August 2004; accepted 19 August 2004

Abstract—A new traceless linker was developed to synthesize a library of 28 compounds possessing an azomethine linkage using combinatorial solid-phase parallel synthesis. The loading of the substrates on a solid support and cleavage from the solid support were performed by an imine synthesis and by imine-exchanged process in the mild conditions, respectively. Products with a thioester group exhibited liquid crystalline properties with the higher transition temperatures than the others.

Many types of linkers were recently developed in combinatorial solid-phase syntheses because the selection of an adequate linker is important to efficiently build the desired libraries.[1] The linker must be stable during the reactions and cleavable without damage to the product at the final stage. In addition, the development of traceless linkers[2] is highly advantageous because the point of attachment on the solid support is not apparent in the target molecules.

Liquid crystals are widely used in optoelectric devices and electron-transporting materials. Considerable synthetic effort and time are required to develop new liquid crystals. We previously demonstrated an efficient combinatorial synthesis to search for new liquid crystals and to systematically investigate the substitution effect on mesomorphism by preparing liquid crystalline libraries for on a solid support.[3–6]

In this paper, we focus on the development of a new traceless linker to synthesize rod-shaped azomethine derivatives, which are typical liquid crystals.[7] The structure of the target molecules **1** synthesized on the solid phase is shown in Scheme 1. They are composed of a rigid aromatic core with an azomethine linkage, an alkoxy side chain, and an ester group. We planned to



Scheme 1. Synthetic plan of an azomethine-type liquid crystalline library.

Keywords: Liquid crystals; Combinatorial synthesis; Traceless linker; Azomethines.

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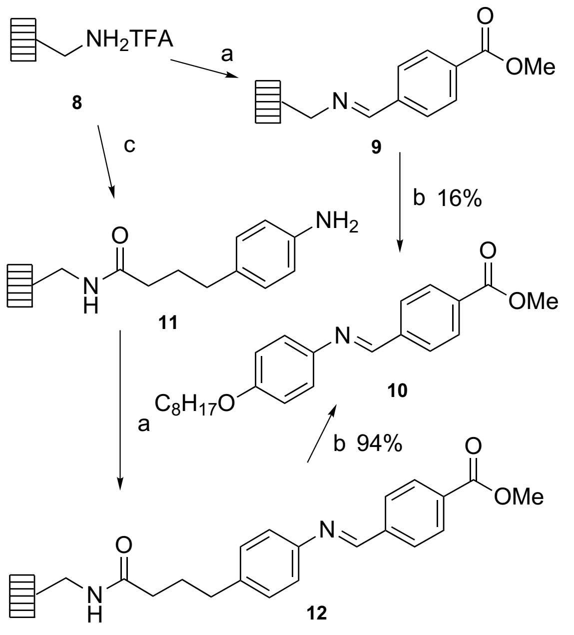
doi:10.1016/j.tetlet.2004.08.106

construct a liquid crystalline library through solid-phase synthesis by employing imine-exchange reactions[8] because the target molecules **1** have no extra functional groups to attach to the solid support. In addition, because the azomethine linkage is labile to acids and bases, we designed a new linker suitable for synthesizing the liquid crystals with an azomethine linkage on a solid support under mild conditions. In the first step, *l* members of 4-formylbenzoic acids **2** are condensed with an amine **3** on the solid support to afford resin-bound azomethine **4** (step 1). In the second step, *m* members of alcohols, thiols, and amines **5** are reacted with **4** to give azomethine **6** (step 2). Finally, the azomethines on the solid support are cleaved by *n* members of 4-alkoxyanilines **7** through an imine-exchange process to give **1** (step 3). In the consecutive procedure, $l \times m \times n$ members of compounds are prepared in these three steps.

Methyl 4-formylbenzoate was linked to aminomethylated SynPhase Lantern **8**, a multipin solid support, through imine formation to give resin-bound methyl benzoate **9**. 4-Octyloxyaniline was added to proceed to the imine-exchange reaction, which gave the desired product **10** in 16% yield. To improve the stability and reactivity of the resin-bound azomethine, we developed a new linker **11** from **8** and a 4-(4-aminophenyl)butyric acid derivative. Remarkably, product **10** was obtained in 94% yield from **11** through intermediate **12** (Scheme 2).

Next, 4-formylbenzoic acid was linked to **11** to afford support-bound benzoic acid derivative **13**. The reaction of **13** with two alcohols, a thiol, and an amine gave the corresponding esters **14a** and **14b**, thioester **14c**, and amide **14d**, respectively. Finally, 7 4-alkoxyanilines were reacted with **14a–d** to afford the 28 final products through imine-exchange reactions. Esters **1a4–1a10** (*n* = 4–10), **1b4–1b10** (*n* = 4–10) and thioesters **1c4–1c10** (*n* = 4–10) were obtained in moderate yield after chromatographic purification (Table 1).[9,10] On the other hand, amides **1d4–1d10** (*n* = 4–10) were obtained in low yield, possibly because the imine-exchange reaction between **13** and diisobutylamine partially occurs at this step.



Scheme 2. Model synthesis of azomethines on the solid support. Reaction conditions: (a) methyl 4-formylbenzoate, DMF, rt, 24 h; (b) 4-octyloxyaniline, 50 °C, 3 h; (c) 4-(4-*tert*-butoxycarbonylaminophenyl)butyric acid, DIC, HOBt, DCM, then TFA, DCM.

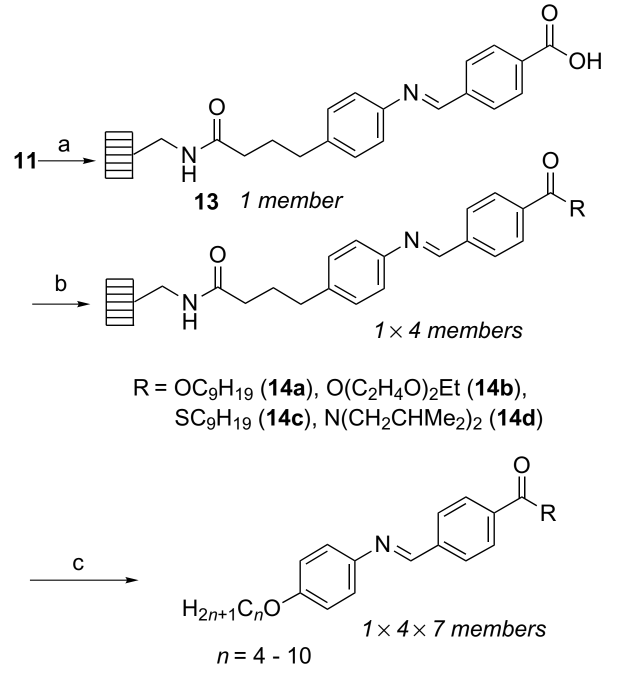
The transition temperature and the thermal behavior of the library members were determined using a polarizing microscope equipped with hot stage and differential scanning calorimetry (DSC) measurement. The results of selected compounds are summarized in Table 1. Esters **1a4–1a10** exhibited smectic A (SmA) and C (SmC) phases, in which the SmA phase was demonstrated by observation of fan and homeotropic textures while the SmC phase was assigned by observation of fan and schlieren textures. The X-ray diffraction study[11] of **1a10** indicated that the layer spacings of the SmA and

Table 1. Isolated yield and transition temperature of the selected library members

Compounds	R^1	*n*	Yield (%)	Transition temp (°C)
1a4	OC_9H_{19}	4	55	Cr·58.7·SmA·81.3·Iso
1a6		6	59	Cr·57.8·SmA·84.3·Iso
1a8		8	66	Cr·63.7·SmA·88.3·Iso
1a10		10	55	Cr·75.1·SmC·80.7·SmA·89.6·Iso
1b4	$O(C_2H_4O)_2Et$	4	71	Cr·74.2·(SmA·42.8)·Iso
1b6		6	57	Cr·62.2·(SmA·40.3)·Iso
1b8		8	52	Cr$_1$·40.0·Cr$_2$·43.5·SmA·46.7·Iso
1b10		10	60	Cr·56.9·Iso
1c4	SC_9H_{19}	4	53	Cr·78.3·SmF·82.9·SmA·150.8·Iso
1c6		6	82	Cr·70.2·SmF·92.7·SmC·111.2·SmA·149.8·Iso
1c8		8	53	Cr·76.9·SmF·102.4·SmC·133.7·SmA·148.7·Iso
1c10		10	33	Cr·90.0·SmF·106.6·SmC·142.6·SmA·146.1·Iso
1d4	$N(CH_2CHMe_2)_2$	4	25	Cr·98.7·Iso
1d6		6	18	Cr·83.3·Iso
1d8		8	20	Cr·105.5·Iso
1d10		10	24	Cr·78.5·Iso

SmC phases were 34.3 Å at 87 °C and 33.8 Å at 78 °C, respectively. Because the calculated molecular length of **1a10** is 37.1 Å, molecules should partially intercalate in the SmA phase and the molecules are tilted 24° in the SmC phase when they form a monolayer arrangement. On the other hand, **1c10** had SmA, SmC, and SmF phases. The SmF phase was assigned by the observation of the mosaic texture. The X-ray diffraction study of **1c10** indicated that the layer spacings of the SmA, SmC, and SmF phases were 33.1 Å at 145 °C, 32.2 Å at 130 °C, and 34.5 Å at 98 °C, respectively. The calculated molecular length of **1c10** is 37.5 Å. The molecular packing models are similar to those of **1a10**. The layer spacing of the tilted SmF phase is slightly larger than that of the SmA phase. It might be because the SmA phase has a more molten side chain than the SmF phase appeared at the lower temperature. Monoethyl diethylene glycol esters **1b4–1b10** had a less stable SmA phase monotropically. The reduction of the thermal stability of **1b4–1b10** might be due to the flexibility of the diethylene glycol chain. The secondary amides **1d4–1d10** were not mesomorphic because of the increase in molecular width due to their branching.

Interestingly, thioesters **1c4–1c10** exhibited liquid crystalline properties with the highest thermal stability compared to **1a4–1a10** and **1b4–1b10**. The thermal stability of the SmA phase of **1c4–1c10**[12] was enhanced by approximately 60 °C when compared with **1a4–1a10**. To explain the thermal stability of thioesters **1c4–1c10**, we calculated the direction and magnitudes of the dipole moment in **1a1** (R = OMe, $n = 1$ in Scheme 3) and **1c1** (R = SMe, $n = 1$ in Scheme 3).[13] Although the difference in the magnitude of the dipole moment of ester **1a1** (2.6 D) and thioester **1c1** (2.8 D) is not so large, the small difference might reflect on the formation of aggregates in the mesophases.



Scheme 3. Synthesis of an azomethine library on the solid support. Reaction conditions: (a) a kind of 4-formylbenzoic acid, DMF, rt, 24 h; (b) four kinds of alcohols, thiol, and amine (n-$C_9H_{19}OH$, Et-$(OC_2H_4)_2OH$, n-$C_9H_{19}SH$, $(Me_2CHCH_2)_2NH$), DIC, DMAP, DCM, rt, 3 h; (c) seven kinds of 4-alkoxyanilines ($n = 4$–10), DMF, 50 °C, 24 h.

In conclusion, we developed a new traceless linker, which made it possible to synthesize a library of liquid crystals with an azomethine linkage using imino exchange reactions through combinatorial solid-phase parallel syntheses. This linker has the advantage of being able to release the final product under mild conditions. In the library, thioesters **1c4–1c10** exhibited smectic phases with higher transition temperatures than esters **1a4–1a10**. Thermal stability of four types of molecules was explained by consideration of the dipole moment of the molecules and flexibility and bulkiness of the substituents of the ester and the amide groups.

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9. General procedures for the synthesis of the library are shown as follows:
Synthesis of **13** *on solid support* **11**: Eighty four pieces of the solid supported aniline **11** (D-series, loading: 38 μmol × 84, 3.19 mmol) were reacted with 4-carboxybenzaldehyde (2.54 g, 16.9 mmol, 5.3 equiv) in DMF solution (80 mL) at room temperature for 24 h. The solution was removed by decantation and the resulting resins were washed with DMF (3 × 0.5 min) and DCM (3 × 0.5 min).
Synthesis of **14a** *on solid support* **13** *with n-nonanol*: Twenty eight pieces of the solid supported azomethine **13** (D-series, loading: 38 μmol × 28, 1.06 mmol) were reacted with 4-*N*,*N*-dimethylaminopyridine (32.5 mg, 0.266 mmol, 0.25 equiv), *n*-nonanol (0.74 mL, 4.2 mmol, 4 equiv), and 1,3-diisopropyl-carbodiimide (1.3 mL, 8.5 mmol, 8 equiv) in DCM at room temperature for 3 h. The solution was removed by decantation and the resulting resins were washed with DMF (3 × 0.5 min) and DCM (3 × 0.5 min).
Cleavage from the solid support: Four pieces of the solid supported ester **14a** (D-series, loading: 38 μmol × 4, 152 μmol) were reacted with 4-*n*-octyloxyaniline (168.2 mg, 0.76 mmol, 5 equiv) in DMF (5 mL) at 50 °C

for 3 h. The the resulting resins were washed with DMF (3 × 3 min). The combined DMF solution was evaporated and purified by HPLC (hexane/EtOAc = 9/1) to give **1a8** in 66% yield (48.3 mg, 107 μmol) as pale yellow solid. All 28 library members have been fully characterized by analytical and spectroscopic means.

10. The yield of the second cycle was almost half of the first one.
11. The X-ray diffraction measurements were carried out using Ni-filtered Cu-Kα radiation at various temperatures.
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13. Compounds **1a1** and **1c1** were chosen as model compounds for **1a4**–**1a10** and **1c4**–**1c10**. Hundred and eight conformers for each compound were generated systematically and individual conformers were optimized at the HF3-21G* level using PC SPARTAN 02 program. Only four conformers were found for **1a1** and **1c1**. The dipole moments calculated from the sum of the Boltzmann factors of each conformation at 298 K.