

Development of a new traceless aniline linker for solid-phase synthesis of azomethines. Application to parallel synthesis of a rod-shaped liquid crystalline library

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Abstract—A new traceless linker was developed to synthesize a library of 42 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 under mild conditions, respectively. Thioesters with a hydroxy group on the central core exhibited liquid crystalline properties with the widest transition temperatures in the library.
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1. Introduction

Solid-phase organic synthesis has been commonly used for combinatorial synthesis to rapidly discover new drugs and materials. 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 Linkers should be easy to load starting materials onto the solid support, must be stable during the reactions and must be cleavable without damage to the product at the final stage. Especially, traceless linkers have advantages because the point of attachment on the solid support is not apparent in the target molecules.²

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 on a solid support.^{3–6}

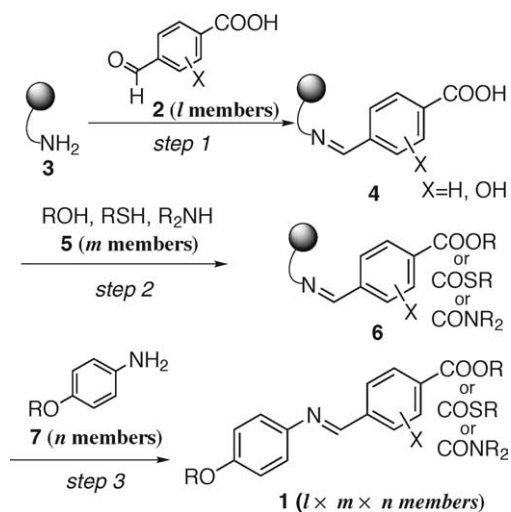
In this paper, we focus on the development of a new

traceless linker to synthesize rod-shaped azomethine derivatives,⁷ which are typical liquid crystals.⁸

2. Results and discussion

2.1. Development of a new aniline linker and synthesis of a liquid crystalline library

The structure of the target molecules **1** synthesized on the



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

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

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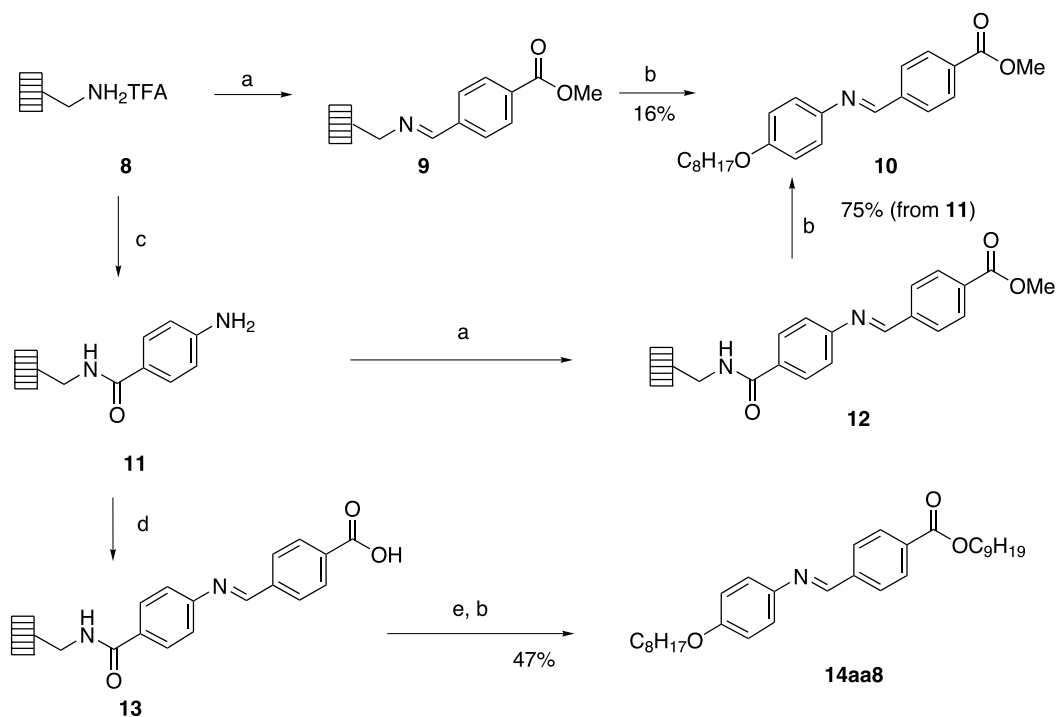
solid phase is shown in Scheme 1. They are composed of a rigid aromatic core with an azomethine linkage, an alkoxy side chain, and an ester or amide group. We planned to construct a liquid crystalline library through solid-phase synthesis by employing imine-exchange reactions⁹ because the target molecules **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 synthesized 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

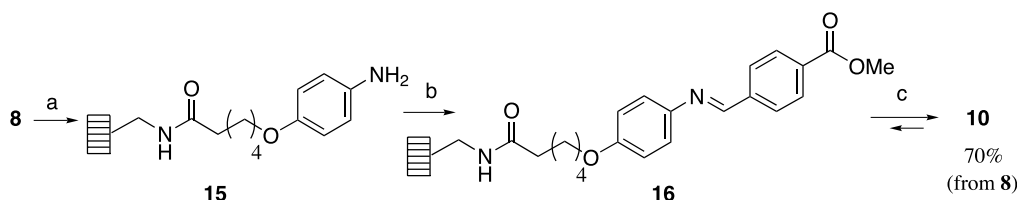
reaction, which gave the desired product **10** in only 16% yield due to the instability of resin-bound azomethine **9**. To stabilize the resin-bound azomethine, we synthesized a linker **11** from **8** and a 4-aminobenzoic acid derivative. The loading of methyl 4-formylbenzoate and cleavage with 4-octyloxyaniline on the resin **12** gave the azomethine **10** in 75% yield. A three-step procedure involving 4-formylbenzoic acid loading followed by condensation with 1-nonanol and cleavage with 4-octyloxyaniline afforded **14aa8** in 47% yield. This reduced yield might result from partial alcoholysis of a resin-bound azomethine **13** during the condensation step. (Scheme 2)

4-Alkoxyaniline linker **15** was synthesized to stabilize a resin-bound azomethine intermediate. Simple loading and cleavage using **15** gave the desired product **10** in 70% yield. The equilibrium between **10** and **16** was not shifted effectively in favor of **10** due to their comparable stability even addition of 4 equiv of 4-octyloxyaniline. (Scheme 3)

The product yields were dependent on the delicate stability balance of the resin-bound azomethine. The ideal linker should resist alcoholysis during condensation and cause an equilibrium shift favorable to the product in the final step.



Scheme 2. Model synthesis of azomethines on a solid support from **8** or **11**. Reaction conditions: (a) methyl 4-formylbenzoate, DMF, rt, 24 h; (b) 4-octyloxyaniline, 50 °C, 3 h; (c) 4-*tert*-butoxycarbonylaminobenzoic acid, DIC, HOBT, DCM, then TFA, DCM; (d) 4-formylbenzoic acid, DMF, rt, 24 h; (e) 1-nonanol, DIC, DMAP, DCM, rt, 3 h.



Scheme 3. Model synthesis of azomethine **10** on a solid support using an aniline linker **15**. Reaction conditions: (a) 6-(4-*tert*-butoxycarbonylaminophenoxy)hexanoic acid, DIC, HOBT, DCM, then TFA, DCM; (b) methyl 4-formylbenzoate, DMF, rt, 24 h; (c) 4-octyloxyaniline, 50 °C, 3 h.

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