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Tetrahedron Letters 45 (2004) 813–815

Tetrahedron Letters

Combinatorial library synthesis of two- and three-ring benzenoid amides on solid support

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Received 12 September 2003; revised 4 November 2003; accepted 7 November 2003

Abstract—A liquid crystalline library of 100 molecules with three benzene rings and 18 molecules with two benzene rings was synthesized on solid support by means of benzoylation or acylation and palladium(0)-catalyzed carbonylation of a secondary amine obtained by a reductive amination of 4-iodoaniline and a backbone amide linker. The conversion and purity of the final products are high enough to investigate the mesomorphic properties.

The conventional rod-like liquid crystals are usually consisted of a rigid core and flexible side chains.[1] The core part is made up of at least two rings such as a phenyl or a cyclohexyl ring in order to keep rigidity of molecules in a mesophase. These rings are connected directly or through a connecting unit such as an ester and an amide group. The flexible side chains bring softness into the molecules. In order to synthesize liquid crystalline compounds, we control these two incompatible factors of rigidity and softness. Usually, we are synthesizing new types of liquid crystals[2] by changing the combination of the rigid core structure and the flexible side chains including the number of rings and the length of the side chains.

Currently, syntheses on solid supports are of great interest for searching new materials such as drugs,[3] bioactive molecules,[4] catalysts, luminescent compounds, and so on.[5] Recently, we reported the first synthesis of new troponoid liquid crystals with an amide-connecting unit on solid support.[6] Very recently, the rapid solution phase synthesis of liquid crystals with fluorinated *p*-quaterphenyls was reported.[7] Thus, the synthesis of liquid crystals using a combinatorial synthetic procedure is still paid much attention. In this paper, we report the synthesis of two- and three-ring benzenoid amides on solid support to demonstrate that the combinatorial synthesis is a useful tool to synthesize new liquid crystals. We chose amide derivatives as the target molecules because we have observed that the amide derivatives have higher transition temperatures than the corresponding ester derivatives[8] and because one of the trivalent arms of the nitrogen atom could be used for the connecting part to a solid support and the amide chromophore was regenerated at the final stage when the final products were removed from the support.

Figure 1 shows the synthetic strategy of benzenoid amides **1** with a two- and three-ring system. Loading on solid support was proceeded by the reaction of a backbone amide linker (BAL) and 4-iodoaniline to form an imine product, which was reduced by $NaBH_3CN$ to give a secondary amine. Acylation or benzoylation on the amino group and carbonylation of the iodo atom with alcohols or 4-alkoxyphenols give products **1** after removal from the solid support. We change the length of the two side chains to make a liquid crystalline library of 100 molecules with three benzene rings and 18 molecules with two benzene rings.

Keywords: Benzenoid liquid crystals; Solid-phase synthesis; Pd-catalyzed carbonylation.

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doi:10.1016/j.tetlet.2003.11.043

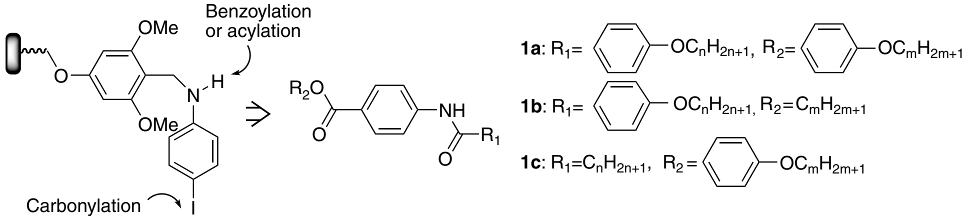
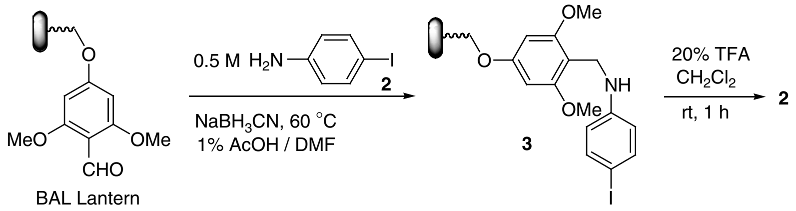


Figure 1. Synthetic strategy.



Scheme 1. Preparation of amine **3** by reductive amination on solid support.

Reaction of a BAL Lantern with 4-iodoaniline (**2**) in the presence of $NaBH_3CN$ gave amine **3** in DMF solution of 1% acetic acid at 60 °C (Scheme 1). The reaction conditions are optimized and the result is shown in Table 1. Conversion and purity were determined by HPLC[9] with the peak area monitored at 254 nm by UV spectroscopy. The conditions of entry 1 are used for the further reaction.

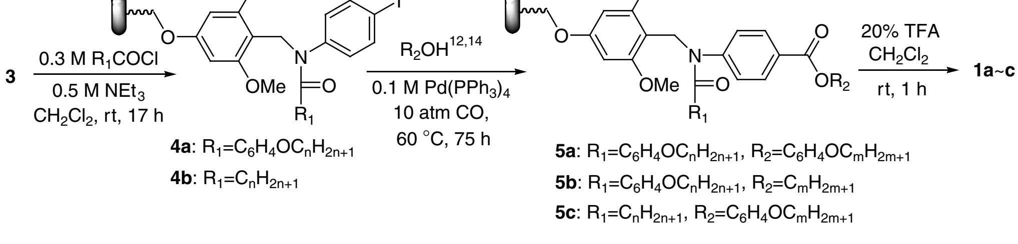
Amine **3** was converted to 4-alkoxybenzamides **4a** with 4-alkoxybenzoyl chlorides in the presence of triethylamine. The conversion was excellent (>99%) and the purity was high. The mass spectral data of benzamide **4a** are satisfied.[10] Carbonylation of benzamide **4a** with 4-alkoxyphenols gave product **5a** in the presence of tetrakis(triphenylphosphine)palladium(0) under 10 atm of carbon monoxide in the presence of 0.5 M of triethylamine.[11,12] Cleavage of **5a** with trifluoroacetic acid gave product **1a** (Scheme 2). The conversion and purity were determined by HPLC.[13] The transition temperatures were determined using a polarizing microscope equipped with a hot stage. Table 2 summarizes the transition temperatures of some selected benzenoid liquid crystals among 118 molecules synthesized on solid support and the authentic samples synthesized in liquid phase. The phase sequence and the transition temperatures are almost identical. When the length of the alkoxy side chain is short, the nematic phases appear. When the length of the alkoxy side chain becomes long, the appearance of nematic phases is decreasing and the smectic A phases are appearing. Finally, the smectic C phases become dominant.

Table 1. Optimization of the reductive amination

Entry	Concentration (M) of $NaBH_3CN$	Time (h)	Yield (%)	Purity (%) of **2**
1	0.05	17	38	>99
2	0.05	34	41	>99
3	0.1	17	35	>99

Similarly, carbonylation of **4a**[14] with alcohol gave **5b**, which was converted to product **1b**. Product **1c** was obtained by acylation of amine **3** with acyl chlorides to give **4b**, carbonylation of **4b**[12] with 4-alkoxyphenols to afford **5c**, and cleavage of **5c** with trifluoroacetic acid. All derivatives with two benzene rings were not mesomorphic. The result of the typical example of **1b** and **1c** is shown in Table 2.

In conclusion, a new benzenoid liquid crystalline library of 100 molecules with a three-ring system and 18 molecules with a two-ring system was constructed. All new compounds **1a** with a three-ring system are mesomorphic whereas products **1b** and **1c** with two benzene rings



Scheme 2. Benzoylation, Pd(0)-catalyzed carbonylation, and cleavage of **5**.

Table 2. Transition temperatures (°C) of benzenoids **1**[a]

	m	n	Synthesized in liquid phase	Synthesized on solid support
1a:	2	2	Cr • 244 • N • 299 • Iso	Cr • 242 • N • 295 • Iso
	2	5	Cr • 208 • SmA • 228 • N • 256 • Iso	Cr • 208 • SmA • 228 • N • 255 • Iso
	2	8	Cr • 208 • SmA • 245 • N • 248 • Iso	Cr • 204 • SmA • 244 • N • 248 • Iso
	5	2	Cr • 212 • SmA • 225 • N • 260 • Iso	Cr • 211 • SmA • 224 • N • 260 • Iso
	5	5	Cr • 198 • SmA • 242 • N • 243 • Iso	Cr • 197 • SmA • 242 • N • 243 • Iso
	5	8	Cr • 192 • SmC • 204 • SmA • 246 • Iso	Cr • 189 • SmC • 202 • SmA • 241 • Iso
	8	2	Cr • 202 • SmA • 255 • N • 256 • Iso	Cr • 195 • SmA • 248 • N • 252 • Iso
	8	5	Cr • 184 • SmA • 243 • Iso	Cr • 182 • SmA • 242 • Iso
	8	8	Cr • 180 • SmC • 188 • SmA • 237 • Iso	Cr • 179 • SmC • 188 • SmA • 234 • Iso
1b:	4	8	Cr • 139 • Iso	Cr • 136 • Iso
1c:	5	9	Cr • 150 • Iso	Cr • 149 • Iso

[a] Determined by microscopic observation. Cr: crystals, N: nematic phases, SmA: smectic A phases, SmC: smectic C phases, Iso: isotropic liquid.

are not mesomorphic. They have high purity and their transition temperatures are almost identical with those of the authentic samples synthesized in liquid phases. The transition temperatures of the three-ring amide **1a** are higher than those of the corresponding esters.[15]

References and notes

1. Demus, D.; Goodby, J.; Gray, G. W.; Spiess, H.-W.; Vill, V. *Handbook of Liquid Crystals*; VCH: Weinheim, 1998.
2. (a) Mori, A.; Takeshita, H.; Kida, K.; Uchida, M. *J. Am. Chem. Soc.* **1990**, *112*, 8635; (b) Mori, A.; Taya, H.; Takeshita, H. *Chem. Lett.* **1991**, 579; (c) Kida, K.; Mori, A.; Takeshita, H. *Mol. Cryst. Liq. Cryst.* **1991**, *199*, 387; (d) Mori, A.; Kato, N.; Takeshita, H.; Uchida, M.; Taya, H.; Nimura, R. *J. Mater. Chem.* **1991**, *1*, 799; (e) Mori, A.; Nimura, R.; Isobe, M.; Takeshita, H. *Chem. Lett.* **1992**, 859; (f) Mori, A.; Takeshita, H.; Nimura, R.; Isobe, M. *Liq. Cryst.* **1993**, *14*, 821; (g) Mori, A.; Taya, H.; Uchida, M.; Takeshita, H. *Chem. Lett.* **1996**, 699; (h) Mori, A.; Taya, H.; Takeshita, H.; Ujiie, S. *J. Mater. Chem.* **1998**, *8*, 595; (i) Mori, A.; Takemoto, M.; Vill, V. *Chem. Lett.* **1998**, 617; (j) Takemoto, M.; Mori, A.; Ujiie, S. *Chem. Lett.* **1999**, 1177; (k) Takemoto, M.; Mori, A.; Ujiie, S.; Vill, V. *Liq. Cryst.* **2002**, *29*, 687; (l) Hashimoto, M.; Ujiie, S.; Mori, A. *Adv. Mater.* **2003**, *15*, 797; (m) Mori, A.; Yokoo, M.; Hashimoto, M.; Ujiie, S.; Diele, S.; Baumeister, U.; Tschierske, C. *J. Am. Chem. Soc.* **2003**, *125*, 6620.
3. (a) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 1; (b) Guiller, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091.
4. Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2288.
5. Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494.
6. Hashimoto, M.; Mori, A.; Inoue, H.; Nagamiya, H.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 1251.
7. Deeg, O.; Bäuerle, P. *Org. Biomol. Chem.* **2003**, *1*, 1609.
8. Hashimoto, M.; Ujiie, S.; Mori, A. *Chem. Lett.* **2000**, 758.
9. The HPLC conditions: Hewlett–Packard series 1100, GL Science Inc. Inertsil ODS-3, 4.6×75 mm, 0.1% HCOOH/H_2O and 0.1% HCOOH/CH_3CN.
10. The MS measurement conditions: Electrospray-TOF MS on a Mariner TK 3500 Biospectrometry.
11. Takahashi, T.; Inoue, H.; Tomida, S.; Doi, T.; Bray, A. M. *Tetrahedron Lett.* **1999**, *40*, 7843.
12. The conditions of the carbonylations: 0.5 M of 4-alkoxyphenol and 0.5 M of NEt_3 in DMF.
13. The HPLC conditions: Hewlett–Packard series 1100, GL Science Inc. Inertsil C8-3, 4.6×75 mm, 20 mM $AcONH_4$/H_2O and CH_3CN.
14. The conditions of the carbonylation: 0.5 M of NEt_3 in alcohol.
15. The transition temperatures of the ester derivatives are shown. $m = n = 2$: Cr • 132 • N • 279.5 • Iso; $m = 5$, $n = 2$: Cr • 129 • N • 239.5 • Iso: $m = n = 5$: Cr • 108 • N • 214 • Iso; $m = 8$, $n = 2$: Cr • 110 • SmA • 130 • N • 213 • Iso; $m = 8$, $n = 5$: Cr • 93 • SmC • 136 • SmA • 156 • N • 200 • Iso; $m = n = 8$: Cr • 87 • SmC • 145 • SmA • 163 • N • 189.5 • Iso. See Vill, V., 'LiqCryst 4.3-Database of Liquid Crystalline Compounds,' Fujitsu Kyushu Engineering, Fukuoka, Japan, 2003.