Pergamon

Tetrahedron Letters 40 (1999) 6041–6044

TETRAHEDRON
LETTERS

Liquid Crystal Control. A Remarkable Enhancement of Both Efficiency and Diastereoselectivity of Intramolecular Thermal Cycloadditions in Smectic Solvents

Kenji Fukunaga and Takehisa Kunieda*

Faculty of Pharmaceutical Sciences, Kumamoto University
5-1 Oe-honmachi, Kumamoto 862-0972, Japan

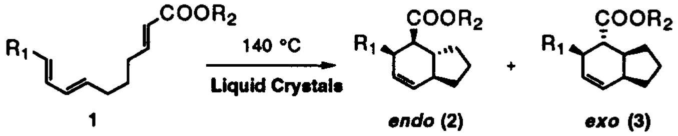
Received 24 May 1999; accepted 9 June 1999

Abstract: The uncatalyzed intramolecular [4+2]cycloaddition of 2*E*,7*E*,9(*E*)-decatrienoates, conducted at 140 °C in a medium of smectic liquid cryctals proceeds with a remarkably high level of chemical efficiency and diastereselectivity, in contrast to the isotropic phase reactions which result in much lower yield and selectivity.

The remarkable effects of liquid crystals, as the reaction medium, on the reactivity of dissolved solutes has been the subject of extensive study over the past few decades.[1] This interest is due, in part, to the similarities of these systems to the microstructures in biological systems,[2] as well as the technological interest. This is in spite of the fact that the accumulated reports are discouraging and offer little hope for the significant chiral control of the asymmetric reactions by mesogens.[3] It is generally recognized that liquid crystalline solvents are able to affect the efficiency and stereochemistry of uni- and bimolecular reactions as the result of size/shape considerations on transition-state dynamics as well as reactant orientational effects, which are heavily dependent on a variety of electronic and conformational factors.[4] The use of liquid crystals to control reactivities has been most effectively demonstrated for the case of unimolecular photochemical reactions,[5] while only few thermochemical reactions which have been conducted at elevated temperatures appear to have been directly affected by the molecular rigidity of liquid ctystals, except for a few carefully designed cases.[6]

In this paper, we wish to report a promising potential of smectic solvents for controlling the stereochemical course of unimolecular thermal reactions with considerably high levels of chemical efficiency and stereoselectivity, compared to structurally similar isotropic media.

The intramolecular uncatalyzed cycloaddition of 2*E*,7*E*,9(*E*)-decatrienoic (1) and 2*E*,8*E*,10(*E*)-undecatrienoic acid esters **4**,[7] was explored at 140 °C as a probe reaction in liquid crystalline (smectic: *sm* and nematic: *ne*) solvents with a rigid *trans*-1,4-disubstituted cyclohexane core, where the diastereoselectivity and



Scheme 1

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)01200-9

efficiency of the reaction were employed as a criteria for evaluating the ability of liquid crystals to control the reaction. This reaction was found to give bicyclic cycloadducts with a slightly preferential formation of *endo*-isomers in isotropic solutions in the absence of catalysts.[7,8]

Table 1. Uncatalyzed Thermal Cycloadditions of 2*E*,7*E*,9(*E*)-Decatrienoate Esters (1)[a]

Decatrienoates (1)			*endo* (2)/*exo*(3) ratio[b] [Yield (%)][c]		
R$_1$	R$_2$		BPCD (*Sm*)[d]	PCC (*I*)[d]	Mesitylene (*I*)[d]
H	*trans*-CC[e]	(**1a**)	11.0 [90]	2.3 [58]	2.0 [60]
H	*cis*-CC[e]	(**1b**)	6.2 [89]	1.9 [60]	2.0 [62]
H	Cholesteryl	(**1c**)	3.0 [91]	1.9 [60]	2.1 [58]
H	Cyclohexyl	(**1d**)	2.2 [88]	2.3 [59]	1.5 [58]
H	Me	(**1e**)	2.0 [57]	2.0 [60]	1.5 [58]
Cyclohexyl	*trans*-CC[e]	(**1f**)[f]	19.0 [90]	3.3 [60]	2.1 [58]
Cyclohexyl	Me	(**1g**)[f]	3.3 [71]	3.3 [57]	2.3 [62]
Hexyl	*trans*-CC[e]	(**1h**)[f]	13.7 [91]	2.3 [63]	1.9 [54]
Isopropyl	*trans*-CC[e]	(**1i**)[f]	11.0 [89]	3.4 [62]	2.4 [59]

[a] A mixture of **1** at the concentrations of 5*wt* % was stirred under smectic (*Sm*) and isotropic (*I*) solvent phases in argon gas at 140 °C for 12h. [b] Determined by ^{1}H-NMR (500 MHz) analysis as the methyl esters of known stereochemistry. [c] Isolated yield. [d] *Sm*: smectic, *I*: isotropic. [e] CC:4-cyclohexylcyclohexyl. [f] Performed for 24h.

The thermotropic liquid crystals employed in this study as anisotropic media involve rod-like cyclohexane type mesogens such as BPCD (smectic),[9] BOCD (smectic)[9] and CBBB (nematic)[10] which clearly exhibit smectic and nematic phases at the experimentally employed reaction temperature (140 °C). Ester mesogens, such as nematic PBOB[10] and cholesteric CDCB[11] were also examined. Anisotropic phase reactions of a series of 2*E*,7*E*,9(*E*)-trienoic acid esters **1a-i** were performed at 140 °C in the liquid crystalline solvents at low concentrations (less than 10 *wt*%), which was sufficient to maintain the mesomorphic phases of the medium over the reaction period, as evidenced by differential scanning calorimetric (DSC) analysis. Among the ester groups examined, the *trans*-4-cyclohexylcyclohexyl moiety (*trans*-CC) proved to be most effective in giving a significantly high level of *endo*-selectivity and high yield in the smectic BPCD solvent. As can be seen in Table **1**, the smectic phase cycloaddition of *trans*-4-cyclohexylcyclohexyl decatrienoate **1a** in BPCD resulted in an excellent *endo*/*exo* ratio of 11:1 in 90% yield, while the methyl (**1e, g**) and cyclohexyl (**1d**) esters gave poorer diastereoselectivity, as has been found in isotropic media such as PCC[12] and mesitylene. The *cis*-4-cyclohexylcyclohexyl (*cis*-CC) (**1b**) and cholesteryl esters (**1c**) showed moderate selectivity. The most striking example of liquid crystal control was observed for the smectic phase cycloaddition of *trans*-4-cyclohexylcyclohexyl 10-cyclohexyl-2*E*,7*E*,9*E*-decatrienoate **1f** in BPCD. The structurally similar smectic solvent BOCD was equally effective and gave a ratio of 19:1 in 91% yield under identical conditions (Table **2**).

The anisotropic rigidity of the solvent appears to be of crucial importance for the significant enhancement of both diastereocontrol and chemical efficiency. This was clearly shown by the dramatic changes in both the *endo*/*exo* ratios and the chemical yields as a function of reactant concentrations (Figure 1). A sharp decrease was observed beyond the critical concentration of 15 *wt%*, indicative of the abrupt destruction of local liquid crystalline solvent rigidity as revealed by a DSC measurement of the doped mixture (Figure 2). The firm accommodation of the dissolved solutes in the anisotropic environment greatly depressed the thermal decomposition of the cycloadducts, even at 140 °C, and resulted in an appreciable acceleration of the cycloaddition reaction, resulting in excellent yields, while degradation of the products was clearly apparent in isotropic media.

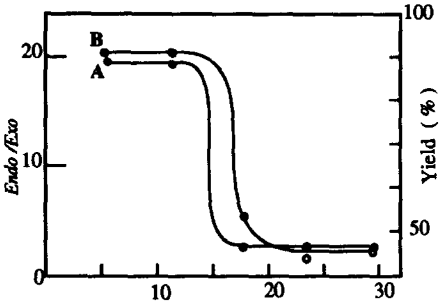


Figure 1. A plot of the *endo*(**2**)/*exo*(**3**) ratio (A) and yield (B) as a function of the concentrations of **1f** in BPCD at 140 °C.

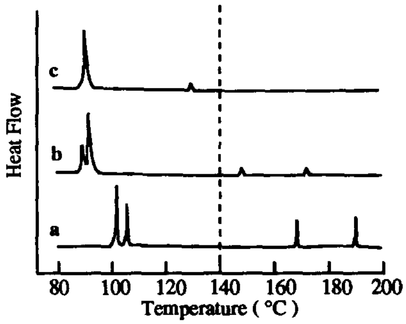


Figure 2. The DSC curves of the **1f**-doped BPCD mixtures. a: 0 *wt%*, b: 5 *wt%*, c: 20 *wt%*

Smectic BPCD environments appear to specifically recognize the transition shape of *trans*-CC esters **1** leading to the *endo*-adducts **2**, which would be incorporated much more effectively in a liquid crystalline matrix, in spite of small differences in structural and electronic features between the transition forms.

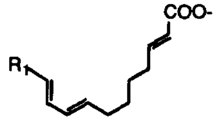
The nematic and cholesteric phase cycloadditions generally resulted in good yields, but the isomeric ratio was much lower, suggesting the importance of a more rigidly ordered smectic type media (Table 2).

Table 2. Thermal Cycloadditions of Trienoates (**1a**, **f**) in Liquid Crystalline Solvents[a]

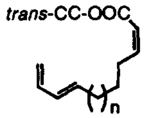
	endo (**2**) / *exo* (**3**) ratio [Yield (%)]			
Compound	BOCD (*Sm*)[b]	CBBB (*Ne*)[b]	PBOB (*Ne*)[b]	CDCB (*Ch*)[b]
1a	11.0 [91]	7.2 [88]	1.9 [79]	1.6 [53]
1f	19.0 [91]	6.8 [87]	2.7 [80]	1.9 [57]

[a] Performed under the same conditions as given in Table 1. [b] *Sm*: smectic, *Ne*: nematic, *Ch*: cholesteric.

The smectic BPCD phase cycloaddition of the *trans*-CC esters **4a,b**[7] proceeded with good chemical efficiency above 89-91% yield, compared to 60% yield in isotropic solvents such as PCC and mesitylene, while no improvement of the diastereoselectivity was observed. On the other hand, the *trans*-CC esters of the 2*Z*-isomers **5** and **6**[7] failed to give high level of liquid crystal effects, in sharp contrast with the 2*E*-isomers **1** and **4**.



4a (R_1=H)
4b (R_1=c-C_6H_{11})



5 (n=1)
6 (n=2)

In conclusion, the molecular ordering which exists in smectic phases may be sufficiently rigid to control the thermochemical intramolecular cycloaddition of **1**, even when the reaction is conducted at 140 °C, with high levels of diastereoselectivity and chemical efficiency, when the reactants are modified, based on a careful consideration of structural similarity to the mesogens and the preferred orientations in a liquid crystalline environment. The concept of liquid crystal control which is entirely based on mesomorphic molecular rigidity appears to be promising, although this type of control is remarkably susceptible to the structural features of the reactants and the mesogens.

References and Notes

1. For reviews, see: (a) Ramamurthy, V. *Tetrahedron*, **1986**, *42*, 5753-839. (b) Weiss, R. G. *Tetrahedron*, **1988**, *44*, 3413-75. (c) Kunieda, T. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 509-16. (d) Leigh, W. J. *Liquid Crystals. Applications and Uses*; Bahadur, B., Ed.; World Scientific: Singapore, **1991**; Chapter 27. (e) Weiss, R. G.; Ramamurthy, V.; Hammond, G. S. *Acc. Chem. Res.*, **1993**, *26*, 530-36.
2. (a) Brown, G. H.; Wolken, J. J. *Liquid Crystals and Biological Structures*; Academic Press: New York, 1979. (b) Bouligand, Y. *Solid State Phys. Suppl. 14*; Academic Press: New York, 1978.
3. (a) Dewar, M. J.; Nahlovsky, B. D. *J. Am. Chem. Soc.*, **1974**, *96*, 460-65. (b) Eskenazi, C.; Nicoud, J. F.; Kagan, H. B. *J. Org. Chem.* **1979**, *47*, 995-999. (c) Dondoni, A.; Medici, A. *Mol. Cryst. Liq. Cryst.*, **1979**, *55*, 47-51.
4. (a) Giroud-Godquin, A. M.; Maitlis, P. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 375-402. (b) Kelker, H.; Hatz, R. *Handbook of Liquid Crystals*; Verlag Chemie: Weinheim, 1980. (c) *Liquid Crystals. The Fourth State of Matter*; Saeva, F. D., Ed.; Marcel Dekker: New York, 1979.
5. For examples, see (a) Hrovat, D. A.; Liu, J. H.; Turro, N. J.; Weiss, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 7033-37. (b) Treanor, R. L.; Weiss, R. G. *ibid.* **1986**, *108*, 3137-39. (c) Zimmermann, R. G.; Liu, J. H.; Weiss, R. G. *ibid.* **1986**, *108*, 5264-71. (d) He, Z.; Weiss, R. G. *ibid.* **1990**, *112*, 5535-41. (e) Workentin, M. S.; Fahie, B. J.; Leigh, W. J. *Can. J. Chem.*, **1991**, *69*, 1435-44.
6. (a) Samori, B.; Fiocco, L. *J. Am. Chem. Soc.* **1982**, *104*, 2634-36. b) De Maria, P.; Lodi, A.; Samori, B.; Rustichelli, F.; Torquati, G. *ibid.* **1984**, *106*, 653-56. (c) Hiraoka, S.; Yoshida, T.; Kansui, H.; Kunieda, T. *Tetrahedron Lett.*, **1992**, *33*, 4341-4344. (d) Kansui, H.; Kunieda, T. *ibid.* **1995**, *36*, 5899-5902. (e) Kansui, H.; Hiraoka, S.; Kunieda, T. *J. Am. Chem. Soc.* **1996**, *118*, 5346-5352. (f) Fukunaga, K.; Kansui, H.; Taniguchi, T.; Kunieda, T. *Tetrahedron Lett.* **1997**, *38*, 8731-8734.
7. (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200-5211. (b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825-4829. (c) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269-2283.
8. A series of 2*E*,7*E*,9-decatrienoates and 10-cyclohexyl-2*E*,7*E*,9*E*-decatrienoates were heated in mesitylene at 140 °C for 12-24h to give, in our hands, the 2-3:1 mixture of **2** (*endo*) and **3** (*exo*) in less than 60% yield.
9. Neubert, M. E.; Ferrato, J. P.; Carpenter, R. E. *Mol. Cryst. Liq. Cryst.* **1979**, *53*, 229-252. BPCD (101-*sm*B-105-*sm*A-173-*ne*-193 °C): bis(4-pentyloxyphenyl)*trans*-1,4-cyclohexanedicarboxylate. BOCD (93-*sm*B-111-smC-119-*sm*A-178 °C): bis(4-octyloxyphenyl) *trans*-1,4-cyclohexanedicarboxylate.
10. Dewar, M. J. S.; Goldberg, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 1582-1586. CBBB (129-*ne*-157 °C): *trans*-1,4-cyclohexylene bis(4-butoxybenzoate). PBOB (118-*ne*-192 °C): 1,4-phenylene bis(4-octyloxybenzoate).
11. CDCB (130-*ch*-213 °C): cholesteryl 2,4-dichlorobenzoate.
12. PCC (mp 34 °C): 4-pentyloxyphenyl cyclohexanecarboxylate.