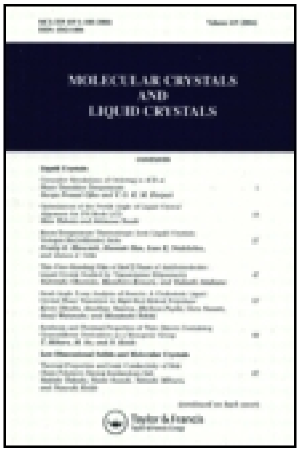

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A Protection-Deprotection Method for the Synthesis of Substituted Benzoyloxybenzoates

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Common syntheses of phenyl benzoyloxybenzoates generally produce products in low yields. A variety of synthetic pathways were employed in an attempt to increase the overall yield of the final product. It was found that catalytic agents such as boron trifluoride-etherate ($BF_3 \cdot Et_2O$), 1,3-dicyclohexylcarbodiimide (DCC), and 4-N,N-dimethylaminopyridine (DMAP) were relatively ineffective in these processes. However, protection of the hydroxy moiety of an appropriately substituted benzoic acid with methyl chloroformate, followed by esterification under normal conditions, and deprotection with ammonia in ethanol produces the hydroxy-benzoyloxybenzoate intermediate. This material can be used in further esterifications to produce phenyl benzoyloxybenzoate compounds in good yield. Materials such as the triply reentrant compound 4-n-nonyloxyphenyl 4-nitrobenzoyloxybenzoate ($DB9ONO_2$) can be prepared by this method.

INTRODUCTION

Mesogenic materials which incorporate the benzoyloxybenzoate moiety in the central aromatic core of their molecular structures have been found to produce both useful and unusual liquid-crystalline properties. For example, incommensurability in certain smectic phases and reentrancy of the nematic phase have been observed in the 4-n-alkoxyphenyl 4-nitrobenzoyloxybenzoates ($DBnONO_2$'s),[1,2] and ferroelectric[3] and pyroelectric[4] properties are exhibited in homologous series such as the S-3,7-dimethyloctyl 4-n-alkoxybenzoyloxybenzoates.[5]

In order to make detailed physical studies of these types of phenomena it is often desirable to have reasonably large quantities of these materials available for investigation. However, common synthetic pathways to these materials do not generally produce the product in high yield.

RESULTS AND DISCUSSION

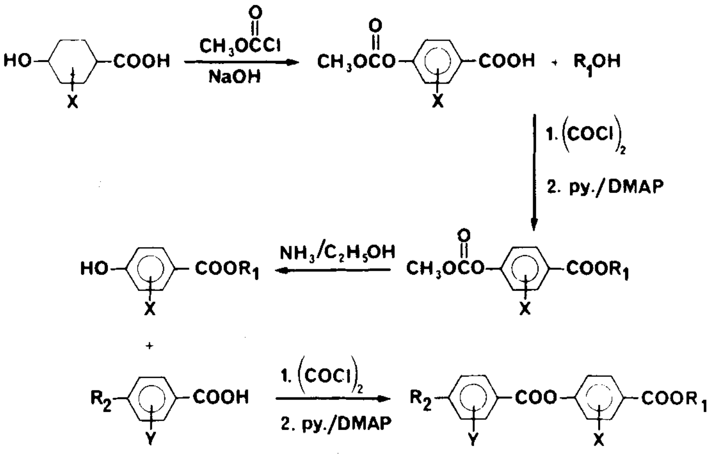
In the preparation of appropriately substituted phenyl benzoyloxybenzoates two alternative approaches are often utilized; one via the production of the substituted phenyl 4-hydroxybenzoate intermediate,[6] or the second by the synthesis of the substituted benzoyloxybenzoic acid intermediate.[7] In the first case esterification is often achieved by reacting the hydroxybenzoic acid with a substituted phenol and employing a suitable catalyst such as 1,3-dicyclohexylcarbodiimide/4-N,N-dimethylaminopyridine (DCC/DMAP),[8] or boron trifluoride-etherate ($BF_3 \cdot Et_2O$), or conc.sulphuric acid/boric acid (H_2SO_4/ Boric acid),[6] or toluene sulfonyl chloride (TosCl).[9] Generally these reactions are heated under reflux for a number of days in order to drive the reaction to equilibrium. Unfortunately the yields in this synthetic step are usually low. In the second example esterification of the hydroxybenzoic acid with an appropriately substituted benzoyl chloride in the presence of a base such as pyridine, 4-N,N-dimethylaminopyridine (DMAP), or triethylamine yields the required benzoyloxybenzoic acid. However this reaction also produces large quantities of by-products which are often acid anhydrides formed by the reaction of the acid chloride with the acid moiety of the benzoic acid.[7] Moreover separation of the required product from the mixture can be an arduous task. The only example of this reaction taking place in a clean and efficient manner is in the esterification of n-alkanoyl chlorides with the appropriately substituted hydroxybenzoic acid.

An alternative to this synthetic approach is the preparation of a suitably esterified intermediate which can be converted to the benzoyloxybenzoic acid. For example esterification of a substituted 4-hydroxybenzaldehyde with an acid chloride and then a Jones oxidation will yield the benzoyloxybenzoic acid.[10] In practice however, the Jones oxidative procedure also proceeds with some saponification of the previously formed ester. This leads to substantial impurities in the final product. Unfortunately, saponification can become a major problem in the preparation of the 4-n-alkoxyphenyl 4-nitrobenzoyloxybenzoates ($DBnONO_2$'s). The intermediate is 4-nitrobenzoyloxybenzaldehyde, and when subjected to a Jones oxidative procedure, the predominant reaction is in fact saponification. The ease with which saponification takes place may be due to the weakening of the ester linkage caused by the strong electron withdrawing effect of the nitro substituent.

Similar problems are also encountered if the intermediate is a substituted 4-nitro or 4-cyano benzoyloxyacetophenone prepared from 4-hydroxyacetophenone. This intermediate can be oxidized to the substituted benzoyloxybenzoic acid by sodium hypobromite, but again saponification and bromination can be undesirable side-reactions.

One method that was found to be generally applicable to the preparation of a variety of benzoyloxybenzoate derivatives was first proposed by Fischer and Fischer.[11] This method proceeds *via* the protection of the hydroxy substituent of the benzoic acid with methyl chloroformate, then esterification with an appropriate alcohol followed by deprotection using ammonia in ethanol to yield the substituted phenyl 4-hydroxybenzoate, as shown in Scheme 1.

The first step of the reaction sequence, the protection of the hydroxy acid with methyl chloroformate, gave an amost quantitative yield provided that the reaction mixture was maintained between −5° and −15° during the procedure. Similarly the deprotection step also proceeds almost quantitatively provided that the ammonia base used is relatively strong (10-35% ammonia in water), and that the reaction is carried out in ethanol to aid solvation of the reactants. Under these conditions cleavage was found to be twice as efficient than under the conditions used previously.[11] Triethylamine was also tested as the base for cleavage of the protecting function, however, in this case



Scheme I

TABLE I

Acid[b]	Alcohol/ Phenol	Reagent	Product	Overall Yield
HOC_6H_4COOH	2M4OH	TosCl	$HOC_6H_4COO2M4$	40%
HOC_6H_4COOH	2M4OH	H_2SO_4/Boric Acid	$HOC_6H_4COO2M4$	55%
HOC_6H_4COOH	2M4OH	DCC/DMAP	No reaction	—
HOC_6H_4COOH	3M7M8OH	H_2SO_4/Boric Acid	No reaction	—
HOC_6H_4COOH	3M7M8OH	DCC/DMAP	No reaction	—
HOC_6H_4COOH	3M7M8OH	TosCl	No reaction	—
HOC_6H_4COOH	$HOC_6H_4OC_9H_{19}$	H_2SO_4/Boric Acid	$HOC_6H_4COOC_6H_4OC_9H_{19}$	5%
HOC_6H_4COOH	$HOC_6H_4C_7H_{15}$	H_2SO_4/Boric Acid	No reaction	—
HOC_6H_4COOH	$HOC_6H_4OC_7H_{15}$	DCC/DMAP	No reaction	—
HOC_6H_4COOH	2M4OH	$MeOCOCl/NH_3$	$HOC_6H_4COO2M4$	55%
HOC_6H_4COOH	3M7M8OH	$MeOCOCl/NH_3$	$HOC_6H_4COO3M7M8$	60%
HOC_6H_4COOH	3M7M87EOH	$MeOCOCl/NH_3$	$HOC_6H_4COO3M7M86E$	83%
HOC_6H_4COOH	3M7M826EOH	$MeOCOCl/NH_3$	$HOC_6H_4COO3M7M826E$	63%
HOC_6H_4COOH	$HOC_6H_4OC_7H_{15}$	$MeOCOCl/NH_3$	$HOC_6H_4COOC_6H_4H_4OC_7H_{15}$	36%
HOC_6H_4COOH	$HOC_6H_4OC_9H_{19}$	$MeOCOCl/NH_3$	$HOC_6H_4COOC_6H_4OC_9H_{19}$	40%
$HOC_{10}H_6COOH$[a]	$HOC_6H_4OC_{10}H_{21}$	$MeOCOCl/NH_3$	$HOC_{10}H_6COOC_6H_4OC_{10}H_{21}$	35%
$HOC_{10}H_6COOH$[a]	$HOC_6H_4O3M7M8$	$MeOCOCl/NH_3$	$HOC_{10}H_6COOC_6H_4O3M7M8$	34%
$HOC_6H_4CH:CHCOOH$	2M4OH	$MeOCOCl/NH_3$	$HOC_6H_4CH:CHCOO2M4$	45%
$HOC_6H_4CH:CHCOOH$	3M7M8OH	$MeOCOCl/NH_3$	$HOC_6H_4CH:CHCOO3M7M8$	44%
$HOC_6H_4CH:C(CN)COOH$	3M7M8OH	$MeOCOCl/NH_3$	$HOC_6H_4CH:C(CN)COO3M7M8$	40%

where 2M4OH = S-2-methylbutan-1-ol
3M7M8OH = S-3,7-dimethyloctan-1-ol
3M7M86EOH = S-citronellol
3M7M826EOH = geraniol
a-6-hydroxy-2-naphthoic acid
b-acids are usually 1,4 substituted benzoic acids

some saponification of the previously formed ester (step 2) was also detected.

A variety of hydroxy aromatic acids were esterified with both aliphatic and aromatic alcohols by this technique. The method was found to be versatile and generally no undesirable side-reactions were detected. Table I lists some substrates that were investigated.

The intermediate, substituted phenyl 4-hydroxybenzoates produced by this method were then used in further esterifications with acid chlorides to produce the desired liquid-crystalline material. Table II lists a variety of liquid-crystal compounds and their phase sequences produced by this method.

All of the materials prepared except for the nitro and cyano substituted phenyl benzoyloxybenzoates were found to have relatively good stabilities. The nitro and cyano materials (DB7OCN, DB7ONO$_2$, and DB9ONO$_2$) on the other hand were found to decompose rapidly when heated to temperatures in excess of 150°. For example 4-n-heptyloxyphenyl 4'-cyanobenzoyloxybenzoate (DB7OCN) (>99% purity by HPLC) when heated to its clearing point in a nitrogen atmosphere for 30 min. decomposed to give a material of less than 95% purity. Liquid chromatography showed that the compound had fragmented back to the original starting components in its synthesis. The reduced stability of these materials appears to be complimented by the observation that saponification readily occurs during the Jones preparation of the 4-cyano or 4-nitrobenzoyloxybenzoic acid. Furthermore the solid state infra-red spectra of the 4-cyano derivatives do not exhibit the characteristic strong adsorption peak for the cyanide stretching mode at approximately 2200 cm^{-1}. This suggests that the cyanide triple bond is considerably weakened by the negative mesomeric effect of the ester function in the *para* position, see Figure 1. This effect is possibly involved at a molecular level in the formation of incommensurate smectic phases. The dipolar strength of the cyano moiety is reduced by this electronic effect, thus the molecule is more likely to pair with neighboring molecules in a variety of ways in order to alleviate the electron deficiency of the cyano group. The different pairs formed have different overlapping lengths thus causing incommensurabilities in the layered smectic phase, as shown in Figure 2. Similar results are also exhibited in the 4-n-alkoxyphenyl 4-cyanobenzoates where the two phenyl-ring molecules pair in this case to produce tilted smectic phases.[12,13] The isomeric 4-n-cyanophenyl 4'-n-alkoxybenzoates which do not suffer with the opposed ester-cyanide dipolar arrangement simply form nematic and orthogonal smectic A phases.

TABLE II

Compound	Code Name	Transition Temperatures
$C_7H_{15}OC_6H_4OOCC_6H_4OOCC_6H_4NO_2$	$DB7ONO_2$	$\mathrm{Iso} \underset{232}{\leftrightarrow} \mathrm{N} \underset{128}{\leftrightarrow} \mathrm{Ad} \underset{102}{\leftrightarrow} \mathrm{A_1}$ ref 2
$C_7H_{15}OC_6H_4OOCC_6H_4OOCC_6H_4CN$	DB7OCN	$\mathrm{Iso} \underset{247}{\leftrightarrow} \mathrm{N} \underset{183}{\leftrightarrow} \mathrm{Ad} \underset{173}{\leftrightarrow} \mathrm{A_1}$ ref 2
$C_9H_{19}OC_6H_4OOCC_6H_4OOCC_6H_4NO_2$	$DB9ONO_2$	$\mathrm{Iso} \underset{224}{\leftrightarrow} \mathrm{N} \underset{195}{\leftrightarrow} \mathrm{Ad} \underset{156}{\leftrightarrow} \mathrm{N} \underset{138}{\leftrightarrow} \mathrm{Ad} \underset{127}{\leftrightarrow} \mathrm{N}$ $\mathrm{N} \underset{124}{\leftrightarrow} \mathrm{A_1} \underset{118}{\leftrightarrow} \tilde{\mathrm{C}} \underset{96}{\leftrightarrow} \mathrm{C_2}$ ref 1
$C_{10}H_{21}OC_6H_4OOCC_{10}H_6OOCC_6H_4O3M7M8$	BSJ1	$\mathrm{Iso} \underset{185}{\leftrightarrow} \mathrm{Ch} \underset{158}{\leftrightarrow} \mathrm{C^*}$
$3M7M8OC_6H_4OOCC_{10}H_6OOCC_6H_4OC_{10}H_{21}$	BSJ2	$\mathrm{Iso} \underset{262}{\leftrightarrow} \mathrm{Ch} \underset{259}{\leftrightarrow} \mathrm{A} \underset{257}{\leftrightarrow} \mathrm{C^*}$
$2M6M7COOC_6H_4COOC_6H_4COOC_6H_4OC_7H_{15}$	703E3B2M6M7	$\mathrm{Iso} \underset{160}{\leftrightarrow} \mathrm{Ch} \underset{131}{\leftrightarrow} \mathrm{C^*}$
$C_{12}H_{25}OC_6H_4COOC_6H_4CH{:}CHCOO2M4$	12OBO2M4C	$\mathrm{Iso} \underset{93}{\leftrightarrow} \mathrm{A} \underset{53}{\leftrightarrow} \mathrm{C^*}$
$C_8H_{17}OC_6H_4COOC_6H_4COOC_6H_4COO2M4$	8O3E3B2M4	$\mathrm{Iso} \underset{171}{\leftrightarrow} \mathrm{Ch} \underset{168}{\leftrightarrow} \mathrm{A} \underset{100}{\leftrightarrow} \mathrm{C^*}$

where
2M4 = S-2-methylbutyl
3M7M8 = S-3,7-dimethyloctyl
2M6M7 = S-2,6-dimethylheptyl
C_6H_4 = 1,4-substituted phenyl ring
$C_{10}H_6$ = 2,6-substituted naphthalene ring system

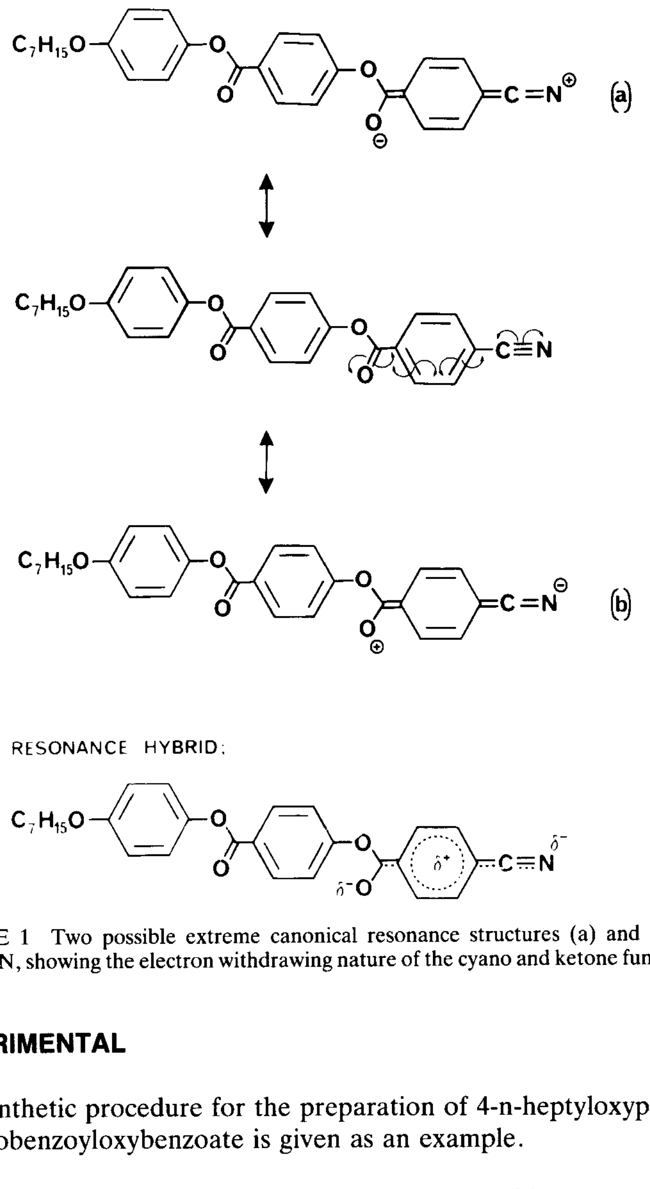


FIGURE 1 Two possible extreme canonical resonance structures (a) and (b) for DB7OCN, showing the electron withdrawing nature of the cyano and ketone functions.

EXPERIMENTAL

The synthetic procedure for the preparation of 4-n-heptyloxyphenyl 4-cyanobenzoyloxybenzoate is given as an example.

1. Preparation of 4-methyoxycarbonyloxybenzoic acid

To a solution of sodium hydroxide (30g, 0.75 mol) in water (800 ml) which was maintained at −10°, 4-hydroxybenzoic acid (35.8g, 0.259 mol) was added with vigorous stirring. Methyl chloroformate (40g, 0.423 mol) was then added slowly to the resulting suspension which

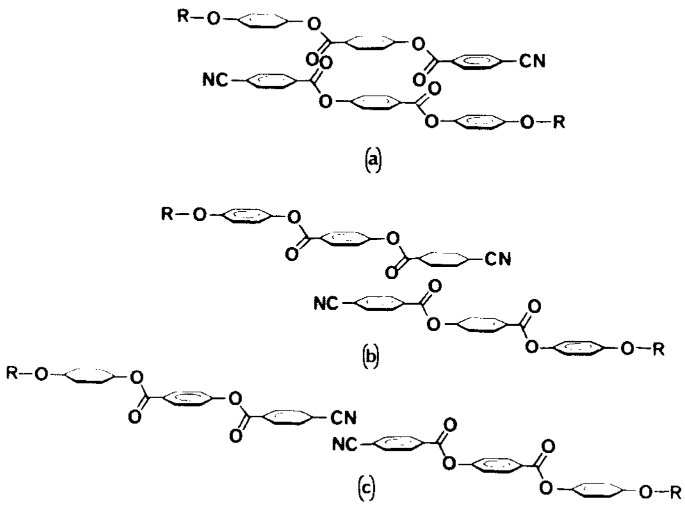


FIGURE 2 Possible packing arrangements for two DBnOCN molecules.

was maintained at −5°. The resulting slurry was stirred for a further 4 hrs. and brought to pH 5 by the addition of conc. hydrochloric acid and water (1:1). The voluminous precipitate was filtered off and recrystallized from ethanol to give a white solid (yield 46g, 90%). mp 84.8° (IR1740, 1670, 1400 820 cm^{-1}, MS m/e 196).

2. Preparation of 4-n-heptyloxyphenol

To potassium hydroxide (11.2g, 0.2 mol) dissolved in water (60 ml), hydroquinone (22.0g, 0.2 mol) was added. The vigorously stirred solution was heated under reflux and 1-bromoheptane (35.8g, 0.2 mol) dissolved in dioxane (40 ml) was added dropwise over a period of 1 hr. The resulting solution was heated under reflux with stirring for 14 hrs. Dioxane was removed by evaporation under reduced pressure and the residue was diluted with water (100 ml). The mixture was brought to pH 5 by the addition of conc. hydrochloric acid and water (1:1). The resulting mixture was extracted with dichloromethane (2 × 150 ml) and the combined extracts were dried over anhydrous magnesium sulfate. The methylene chloride was removed by evaporation under vacuum. The solid residue was recrystallized from hexane (600 ml) to yield an off-white solid (yield 9.25g, 40%), mp 58.5 (IR 3350, 2900, 1500, 1220, 810 cm^{-1}, MS m/e 192).

3. Preparation of 4-n-heptyloxyphenyl 4-methoxycarbonyloxybenzoate

Oxalyl chloride (60 ml) was added slowly to 4-methoxycarbonyloxybenzoic acid (6g, 0.0306 mol) and the resulting solution was heated under reflux with stirring for 3 hrs. The excess oxalyl chloride was removed by evaporation under reduced pressure. 4-n-heptyloxyphenol (6.37g, 0.0306 mol) dissolved in toluene (60 ml), pyridine/4-N,N-dimethylaminopyridine (10:1) (25 ml), was added to the crude 4-methoxycarbonyloxybenzoyl chloride (6.57g, 0.0306 mol). The mixture was heated under reflux for a further 5 hrs. and the cooled solution was evaporated to dryness in vacuo. The residue was purified by column chromatography over silica-gel (60-200 mesh) using methylene chloride/hexane (4:1) as the eluant. The product was recrystallized from petroleum-ether (33–65°) to give a white solid (yield 5.4g, 41%). The product had the following transition temperatures: crystal to nematic, 59°, nematic to isotropic liquid, 92.3°. (IR 2900, 2820, cm^{-1}, MS m/e 386)

4. Preparation of 4-n-heptyloxyphenyl 4-hydroxybenzoate

4-n-heptyloxyphenyl 4-methoxycarbonyloxybenzoate (5.4g, 0.0125 mol) was stirred in a mixture of ethanol (150 ml) and ammonia (10–35%) (75 ml) at room temperature for 1 hr. The extent of the reaction was monitored by thin layer chromatography (silica-gel 60 F_{254}, 0.2 mm, Rf = ~0.2). After the reaction was complete (usually 30 min), the solution was poured into water (200 ml) and cooled in dry ice. The precipitated product was filtered and recrystallized from acetonitrile (yield 4.16g, 89%) mp 166.8 (IR 3880, 2900, 2840, 1690, 1570, 1490, 1150, 1060 cm^{-1}, MS m/e 348).

5. Preparation of 4-n-heptyloxyphenyl 4-cyanobenzoyloxybenzoate

To 4-cyanobenzoyl chloride (0.88g, 0.00534 mol), a solution of 4-n-heptyloxyphenyl 4-hydroxybenzoate (2g, 0.00534 mol), toluene (75 ml) and pyridine/4-N,N-dimethylaminopyridine (10:1) (30 ml) was added, and the resulting mixture was heated under reflux with stirring for 5 hrs. The reaction mixture was reduced to dryness by evaporation under reduced pressure. The residue was purified by column chromatography over silica-gel (60-200 mesh) using methylene chloride/hexane (4:1) as the eluant. The product was recrystallized from acetonitrile (yield 1.23, 46%) and found to have the following transition temperatures: crystal to smectic A_1, 132.4; smectic A_1 to smectic Ad, 173; smectic Ad to nematic, 182.9; nematic to isotropic liquid, 247.2 (IR 2900, 2220 (CN-weak), 1720, 1450, 1070, 760 cm^{-1}, MS m/e 457).

The transition temperatures of the liquid-crystalline products were determined by thermal optical microscopy using a Zeiss Universal polarizing microscope in conjunction with a Mettler FP52 hot-stage and FP5 control unit. The phases were identified by textural and miscibility studies. Transition temperatures were also confirmed by differential scanning calorimetry employing a Perkin-Elmer DSC-4-TADS system. Purities were determined by reverse phase liquid chromatography using a Beckmann 344 system equipped with a variable wavelength UV-VIS detector. The column was constructed of octadecylsiloxane (5 μm pore size, 25 × 0.46 cm).

SUMMARY

A protection/deprotection method for hydroxy substituted carboxylic acids has been developed. The protection and cleavage steps are essentially quantitative making this a useful synthetic tool for the prepartion of substituted phenyl benzoyloxybenzoates, which possess unusual liquid-crystalline properties.

References

1. N. H. Tinn, F. Hardouin and C. Destrade, *J. Phys.* (Paris), **43**, 1127, 1982.
2. F. Hardouin, A. M. Levelut, M. F. Achard and G. Sigaud, *J. Chim. Phys.* (Paris), **80**, 53, 1983.
3. J. W. Goodby and T. M. Leslie, Liquid Crystals and Ordered Fluids, Eds. A. C. Griffin and J. F. Johnson, Plenum, New York, 1984, vol. 4, p. 1.
4. A. M. Glass, J. S. Patel, J. W. Goodby, D. H. Olson and J. M. Geary, to be published.
5. E. Chin, J. W. Goodby, J. S. Patel, J. M. Geary and T. M. Leslie, to be published.
6. W. W. Lowrance, *Tet. Lett.*, **37**, 3453, 1971.
7. W. R. Young, I. Haller and D. C. Green, *J. Org. Chem.*, **37**, 3707, 1972.
8. B. Neises and W. Steglich, *Angew. Chem. Int. Ed.*, **17**, 522, 1978, J. R. Grunwell and D. L. Foerst, *Syn. Comm.*, **6**, 453, 1976.
9. O. N. Bubel, V. S. Bezborodov and P. V. Kuzmichkin, *Vest Beloruss Gos Univ*, Ser. II, p. 2, 1978.
10. See for example, D. J. Pasto and C. R. Johnson, Organic Structure Determination, Prentice-Hall, 1969, p. 363.
11. E. Fischer and M. O. L. Fischer, *Ber. Org. Chem.*, **46**, 1138, 1913.
12. J. W. Goodby, T. M. Leslie, P. E. Cladis and P. L. Finn, Liquid Crystals and Ordered Fluids, Eds. A. C. Griffin and J. F. Johnson, Plenum, New York, 1984, vol. 4, p. 89.
13. P. E. Cladis, P. L. Finn and J. W. Goodby, Liquid Crystals and Ordered Fluids, Eds. A. C. Griffin and J. F. Johnson, Plenum, New York, 1984, vol. 4, p. 203.