Solid-state assisted synthesis of oligobenzoates

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The solid-state assisted synthesis opens an easy access to oligobenzoates end-capped with gallic acid, protocatechuic acid or 4-hydroxybenzoic acid etherified with long flexible chains – which are important precursors for liquid crystalline materials. The latter may consist of aliphatic, oligoethyleneoxy and semiperfluorinated chains. The rapid preparation of oligoesters with different peripheries is demonstrated.

Keywords: solid phase synthesis; oligobenzoates; promesogens; LC precursors; Wang resin; HYCRAM linker

Oligobenzoates and polybenzoates are a class of compounds of great importance, for example in polymer science,[1,2] medicinal chemistry[3,4] and supramolecular chemistry.[5,6] Their self-assembly of the benzoate scaffold is responsible for the high stability of commercial aromatic main chain polymers such as Vectra® [1] and for the formation of various liquid crystal (LC) families (Figure 1).[2,5–16]

Oligobenzoates 1 containing the benzoate scaffold and one to three peripheral flexible chains are often components of soft materials such as LCs or LC polymers.[1,2,7–9] Nanosegregation of different incompatible molecular building blocks is one main driving force to conduct the self-assembly.[17] The scaffolds of different sizes may be used to generate calamitic (4A–C), banana- (4D) or star-shaped mesogens (4E) and also mesogens via supramolecular interactions.[10–16] In order to study the self-assembly of such materials in detail, oligobenzoate units (1–3) with different peripheral chains are needed.

The conventional synthesis starts always from the periphery.[11] Typically gallic acid, protocatechuic acid and 4-hydroxybenzoic acid derivatives are decorated by an ether synthesis with the flexible chains to obtain compounds 5 (Scheme 1). The subsequent reaction with monoprotected 4-hydroxybenzoic acid 6 and cleavage of the protective group affords the enlarged building block (1–3)m. Iterative repetition of this procedure gives the growing oligomer scaffolds (e.g. (1–3)m, m = 1, 2, 3…).[11,12]

This conventional preparation procedure has two important disadvantages: (1) for a given oligobenzoate scaffold the peripheral unit has to be selected at the beginning of the synthesis and each new periphery always needs a complete new preparation; (2) the purification must be performed after each step which becomes increasingly difficult owing to the decreasing solubility of the products with the expanding oligobenzoate scaffold. Moreover, the variation of the peripheral chains or the type of repeating units require not only a new preparation sequence but also new separation and purification procedures, which can be sophisticated especially for peripheral semiperfluorinated or oligoethyleneoxy chains.[18] Therefore, we aimed to develop a solid-state assisted synthesis of such molecules which allow assembling the molecular scaffold from the inner repeating unit to the periphery with the flexible chains. This procedure will permit the generation of oligomers with different types and numbers of repeating units with a protected hydroxy and a carboxy functionality.

The synthesis is eventually completed by the coupling of a peripheral building block. The latter step can be performed with various flexible chain-bearing components after dividing the polymer support in separated lots. That results in arms with the same internal scaffold but with different peripheries. Only in the final step after cleavage from the resin purification procedures have to be optimised. Thus, a library of arms may be easily accessible in the scale of 0.5–1.0 g, which is sufficient for most of the studies to determine materials properties. Solid-state assisted synthetic methods have been employed earlier for the synthesis of libraries of liquid crystals.[19] An elaborated direct synthesis of calamitic benzoylaminobenzoates and banana-shaped oligobenzoates based on an amid or a

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traceless linker have been recently presented using a Pd-catalysed carbonylation.[20,21] Large libraries of 16–100 liquid crystalline compounds have been produced, however, only in small quantities.

Here, we present an easy and cheap parallel solid phase synthesis of oligobenzoates \((1-3)_p^m\) \((n = 1,2,3\ldots)\) with a defined number of repeating units \(n\) and type and number \(p\) of peripheral flexible
chains on a Wang resin. The synthesis of oligomers on a polymer support always needs a linker to the polymer, which has to be stable under the synthetic procedures and can be selectively cleaved at the end. The commercially available, inexpensive Wang resin needs for the final cleavage procedure the treatment with trifluoroacetic acid (90%). Under these conditions, however, the oligobenzoates are reported to be reactive.\[22\] Therefore, we have initially chosen the hydroxycrotonylaminomethyl (HYCRAM) linker which has been described to cleave under neutral conditions with weak nucleophiles and Pd(0) as the catalyst.\[23\] This reaction sequence requires an aminomethyl functionalised resin and the synthesis and coupling of the HYCRAM linker as additional preparation steps (Scheme 2, Method B). Unfortunately, our first test-product \(1_{3}^{1}\) could not be completely separated from the catalyst after the cleavage from the resin which made this method less practical.\[24\]

Therefore, we recently tried the synthesis of a small oligobenzoate \(1_{3}^{1}\) directly at the Wang resin and surprisingly isolated the final product in high yield (Table 1). Evidently, the cleaving procedure did not affect the ester bonds of the oligomer. This finding opens an easy access to aromatic oligoesters and its derivatives, which we explored here for series of parent oligobenzoates end-capped with flexible chains.

The optimised synthesis is shown in Scheme 2 (Method A). The key compound of the synthesis is the hydroxybenzoic acid \(8\) which is protected by the tert-butylidemethylsilyl (TBDMS) group at the hydroxy side. This compound can be easily obtained by silylation of the commercial available benzyl

![Scheme 2](image-url)
4-hydroxybenzoate 6 and subsequent hydrogenation and cleavage of the benzy1 group. The solid-state assisted synthesis begins with the coupling of compound 8 to the Wang resin S7a and cleavage of the TBDMS group by TBAF to yield S8a1. Repeated coupling and cleavage (Steps 1 + 2) result in the iterative elongation of the benzoate sequence S9a m+1.

Eventually, the peripheral group 5 with a defined number of flexible chains is attached and the product is cleaved by TFA from the resin (Method A). A typical procedure to obtain 13 is given in Table 1. Excluding the swelling procedure as preparation step of the resin, the synthesis comprises four steps and the final purification. Only the coupling of the peripheral unit and the last purification step has to be adapted according to the solubility of the peripheral groups and products. After cleavage of the product from the resin it appears that the products are often almost sufficiently pure which is documented by NMR and elemental analysis (Figure 2 and supplemental data).

The conventional synthesis needs the isolation from the reaction mixture in each individual step. In case of the derivatives 1 with aliphatic chains in the periphery, the compounds readily precipitate from acetone; thus, for those materials the solid phase synthesis is only of advantage if compounds with different oligobenzoate scaffolds or various peripheries – different length or number of aliphatic chains – are needed in quantities of about 1 g. For this purpose the total work load is minimal since purification of a rather pure crude product has to be done only once. A large amount (>10 g) of one specific oligomer 1 can be synthesised by this method too using the parallel synthesis in up to 16 vessels provided by our machine (see supplemental data) but this maybe more conveniently and cheaply prepared by

| Comp. | Yield [%] | Steps/Isolation | Ref. | Yield [%] | Steps/Isolation |
|-------|-----------|-----------------|------|-----------|-----------------|
| 1,2   | 73        | 2/2             | [11] | 66        | 4/1             |
| 1,2   | 52        | 4/4             | [25] | 67        | 6/1             |
| 1,2   | 83        | 4/4             | –    | 35        | 6/1             |
| 1,2   | 61        | 4/4             | [12] | 48        | 6/1             |
| 2,1   | 66        | 2/2             | –    | 92        | 4/1             |
| 2,1   | 43        | 2/2             | –    | 92        | 4/1             |
| 2,1   | 25        | 4/4             | –    | 89        | 6/1             |
| 2,1   | 7         | 4/4             | –    | 86        | 6/1             |
| 3,1   | –         | 4/4             | –    | 35        | 6/1             |

Table 1. Yields of the solid phase and the conventional synthesis.

Typical procedure

Preparation
1.0 g Wang resin (1.10 mmol/g) is swollen for 2 h at RT in 15 ml DCM and subsequently washed with 2 × 15 ml DCM

Step 1 Coupling of the repeating unit:
2 eq protected 4-hydroxybenzoic acid, 0.8 eq DPTS and 15 ml DCM are added and after five minutes shaking 2 eq DIC are given to the mixture which is shaken subsequently for 12 h. Then the solution is removed by filtration

Washing procedure:
The resin is washed with 15 ml DCM, 15 ml methanol and 15 ml DCM

Step 2 Cleavage of the silyl group:
The vessel with the resin is charged with 3 eq TBAF, 3.5 eq acetic acid and 15 ml THF and shaken for 2 h at RT before the solvent is removed by filtration

Washing procedure (see Step 1)

Step 3 Coupling of the peripheral unit:
2 eq 3,4,5-tridodecyloxybenzoic acid, 0.8 eq DPTS, 15 ml DMF: DCM (2:1) and – after five minutes shaking – 2 eq DIC are added and the mixture is shaken for 12 h. The solution is removed by filtration

Washing procedure (see Step 1)

Step 4 Cleavage from the resin:
The resin is shaken for 2 h with 15 ml of a cleavage solution (90% TFA, 7.5% triethylsilan, 2.5% water). After filtration the resin is washed twice with 15 ml DCM. The solvent of the combined liquids is removed in vacuum

Isolation
Individual purification

Notes: X, n = number of repeating units, p = number of chains, X = compound number and the type of chains; 1: R = dodecyloxy, 2: R = oligoethyleneoxy, 3: R = 1H, 1H, 2H, 2H, 3H, 3H, 4H, 4H-perfluorododecyl, DCM dichloromethane.
the conventional synthesis. However, inspection of Table 1 shows that the solid phase synthesis becomes superior in the series of oligoethyleneoxy derivatives 2. These are compounds which are very difficult to crystallise or purify by chromatography. Thus loss of material will be faced in each individual step and the total yields are much lower compared to the solid-state assisted synthesis. Owing to the excellent solubility of the peripheral groups the products obtained by Method A can be isolated in very high overall yields up to 92% (\(2^1\)) and 89% (\(2^2\)). For derivatives of series \(2^1\) and \(2^2\) this is an average yield of 98% for each individual synthetic step. It should be stressed that after cleavage from the resin and evaporation of the liquids the products were analytically pure without further purification. Figure 2 highlights the \(^1\)H NMR spectrum of \(2_{3^2}\) as an example showing the signal sets of two AA'BB' systems and a singlet for the protons at the peripheral group. The integration is in perfect agreement also with the signals attributed to the three oligoethyleneoxy chains.

Table 1 exhibits that the method can also be extended to products with semiperfluorinated chains (3\(_{3^2}\)). Compounds 5 with semiperfluorinated chains possess often a low solubility in conventional organic solvents and therefore multistep synthetic procedures are demanding. The solid phase method displaces these challenges to the final step. After cleavage, the product is analytically pure (see supplemental data).

In conclusion, a simple solid-state assisted synthesis of oligobenzoates with various peripheral chains (alkyl, oligoethyleneoxy, semiperfluorinated chains) has been shown successfully on a Wang resin. The work load is lower compared with a conventional synthesis for which the intermediate products have to be isolated in each step. The yields are superior for derivatives containing oligoethyleneoxy chains. If the amount of material needed does not exceed 1–2 g or a variation of chains or oligobenzoate scaffolds are needed, this type of synthesis seems to be the most convenient synthetic method towards oligobenzoate building blocks. Work is in progress to optimise reaction conditions in the final step for derivatives with semiperfluorinated and siloxane chains.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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**Supplemental data**

Supplemental data for this article can be accessed here.

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