The synthesis of unsymmetrically substituted triphenylenes through controlled construction of the core and subsequent aromatic substitution reactions – a perspective and update

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Abstract

George Gray was enthusiastic about the emergence and scientific developments in the field of discotic liquid crystals, taking particular interest in our early work to develop new synthetic methods to widen the area. In this article an overview of the strength and versatility of the synthetic chemistry is presented, along with two updates. The first describes a simple modification that allows easy preparation of 2,3-dialkoxytriphenylene without over-reaction, and the second highlights another unexpected synthesis outcome where bromination and nitration of a tetraalkoxytriphenylene precursor leads to two different regiochemical outcomes.

1. Foreword (by Andrew Cammidge)

In 1992 I began a postdoctoral fellowship at the University of Leeds under the joint supervision of Richard Bushby and Neville Boden. My interview for this post had taken place by telephone between Leeds and America, and so I had not even met Richard or Neville before my first day. The 3 years I spent at Leeds were truly formative – the field of discotic liquid crystals was moving rapidly and the first signs of potential applications were emerging. Most importantly for me, however, was the dynamic and philosophy within our project. Neville and Richard encouraged and allowed freedom and independence – an approach that I continue in my own research group. Two major synthetic breakthroughs came during this period. The first was extension of the straightforward synthesis of triphenylene discotics to unsymmetrical derivatives (and polymers). The second was the functionalisation of triphenylene discotics through electrophilic aromatic substitution. I recall the first reaction well; in fact the full sequence from idea to breakthrough result took less than 48h. A few minutes after having the idea I dissolved a small sample of hexakis(hexyloxy)triphenylene (HAT6) in ether (in a test tube!) added a few drops of acetic acid and nitric acid. Tlc analysis showed a single product. I performed the reaction “properly” isolating nitro-HAT6 that displayed columnar liquid crystal behaviour across a wide temperature range. Rapid functional group interconversion was easily achieved to give a new series of materials.

The two synthetic breakthroughs led to my first meeting with George Gray. The synthetic chemistry developed at Leeds was straightforward and furnished high-purity materials through protocols that could be scaled. Alongside their emerging potential in applications, this made them attractive to Merck Ltd. George was instrumental in developing this relationship to Merck, and he hosted Neville, Richard and I at Merck and his home. During this time his scientific enthusiasm was matched by his warmth and welcome – both equally inspiring for a young aspiring researcher. I left Leeds in 1995 to begin my fully independent academic career (although maintaining contact and collaboration with Neville and Richard at Leeds). George was again instrumental in cementing my relationship with Merck and actively supported my career in its early stages. Whenever we met up at conferences or events (a Discotic Liquid Crystals conference in Trieste is particularly memorable), he was keen to catch up on my latest progress and give his enthusiastic support. Above all, he was always great company.

1. Introduction

The triphenylene nucleus has proved a versatile core for the investigation of mesogenic behaviour in discotic systems (Figure 1).[1-3] Synthetic chemistry has been developed to access complex unsymmetrical derivatives, for both applications and to probe liquid crystal behaviour. Our group has focused on two areas that combine to deliver multifunctional triphenylenes. The first concentrates on assembling the triphenylene core itself (Scheme 1), with appropriately positioned substituents. The combination of coupling and cross-coupling methods, followed typically by oxidative cyclisation, leads to the final triphenylene product [4-10]. In most examples the sequence assembles an orthoterphenyl (often by palladium catalysed Suzuki-Miyaura cross-coupling) which is converted to the triphenylene by treatment with ferric chloride. This method was employed to give triphenylenes bearing 4 and 2 alkoxide side chains,[10] contrasting the archetypal hexaalkoxytriphenylene discotics (the HATn series).

Figure 1

Scheme 1

Di- and tetra-alkoxytriphenylenes (Scheme 2) have proved excellent precursors for our second main functionalization strategy – simple electrophilic aromatic substitution. [10-13] Bromination [10] is generally straightforward, and yields (tetra- or di-) bromides, themselves acting as substrates for further substitution [10] and cross-coupling reactions.[14-17] Following these sequences, numerous families of triphenylene derivatives have been prepared and investigated. Tetraalkoxytriphenylenes bearing additional functionality at the 3,6-positions have proved particularly useful and intriguing. Columnar mesophase behaviour is preserved in simple systems and various diverse functional groups can be accommodated so long as they are able to conjugate with the triphenylene pi-system. [17]

Scheme 2.

The 3,6-substuitution pattern also allows more elaborate functional structures to be targeted and we have designed and synthesised rigid twinned architectures.[18-20] Twins such as **17** [18] and **18** [19] display the relatively rare discotic nematic mesophase, [21] likely imposed by space-filling constraints in the condensed phases (Figure 2).

1. Discussion

In this paper we provide two updates to our strategies for constructing and functionalising alkoxytriphenylenes. In our earlier work on the construction of dialkoxytriphenylenes [10] we encountered a problem accessing one member of the series (2,3-dialkoxytriphenylene **21**). Construction of the precursor ortho terphenyl **19** was straightforward but oxidative cyclisation using ferric chloride led to exclusive isolation of dichloride product **20**, resulting from further reaction of the formed triphenylene product.[10] Chlorides are poor substrates in cross-coupling reactions so this unwanted reaction presented a significant drawback. Previously the conversion of ortho terphenyl **19** into the dialkoxytriphenylne **21** has been achieved by photochemical cyclisation/oxidation. [10, 22, 23] Although this strategy works well for the synthesis of triphenylenes it is slow and difficult to scale up.

There is little doubt that the ferric chloride mediated cyclisation of **19** initially leads to the formation of the desired triphenylene **21**. Our recent reinvestigation of this reaction therefore focused on developing conditions to stop the reaction at this stage. In fact this is easily achieved. Our previous conditions [10] tended to use FeCl3 in large excess and the exothermic nature of the reaction causes its temperature to rise in the early stages. Performing the reaction using 5 equivalents of ferric chloride and controlling the temperature of the reaction and workup leads smoothly to formation of dialkoxytriphenylene. The product is isolated in high yields following a simple methanol workup (scheme 3).

Scheme 3.

As introduced previously, we have paid particular attention to alkoxytriphenylenes that bear additional functional groups at the 3,6-positions. Appropriate substitution at these sites allows conjugation through the triphenylene pi-system but the substituents are held far apart. In the case of strained twins like dehydroannulene structures **17**, this leads to interesting properties while retaining molecular stability. The synthetic chemistry is relatively straightforward – in particular the bromination [10] that we have employed widely in the synthesis of derivatives proceeds smoothly at room temperature. However, electrophilic aromatic substitution on alkoxytriphenylenes is not always a predictable process. Furthermore the mechanisms of such substitutions do not always follow accepted SEAr pathways. For example, whereas the single nitration of HAT6 (the first electrophilic aromatic substitution reaction on discotic triphenylenes that we reported) proceeds smoothly [11] and easily, chlorination reactions with FeCl3 (described above) and iodine monochloride [24] provide two examples where multistep pathways are followed (Scheme 4). Multiple substitution also potentially leads to mixtures of isomeric products. [25, 26]

Scheme 4.

Here we report a further example of unexpected product formation in electrophilic aromatic substitution reactions on triphenylene substrates. As part of our ongoing work on triphenylene twins linked through the 3,6-positions we attempted the direct nitration of tetraalkoxytriphenylene **9**, knowing the comparable bromination reaction was straightforward (to give **10)**. The nitration conditions initially followed the procedure developed for nitration of hexaalkoxytriphenylenes (Scheme 4) [11] – tetraalkoxytriphenylene was dissolved in ether-acetic acid and concentrated nitric acid was added dropwise. However, unlike the nitration of HAT6, and bromination of **9**, no reaction occurred at room temperature. Heating the reaction mixture at reflux for 16 h, however, led to smooth formation of a dinitrotriphenylene product as a single regioisomer. Initial analysis of the 1H NMR spectrum showed the product to have high symmetry, but it did not correspond to that expected for the 3,6-dinitrotriphenylene isomer (where 3 x singlet signals would be expected in the aromatic region). The structure was tentatively assigned as dinitrotriphenylene **24** and this assignment was subsequently proved by further synthetic modification. The dinitrotriphenylene product was reduced using tin powder in refluxing acetic acid and the resulting diamine **25** was treated straightaway with an excess of acetyl chloride in chloroform/pyridine. The corresponding diimide **26** was isolated as a crystalline solid, and crystals suitable for X-ray crystallography were subsequently grown (Scheme 5). The analysis confirmed the regiochemical assignment of the product, and hence the structure of dinitrotriphenylene **24**. the difference in regiochemical outcome between bromination and nitration is remarkable – each process produces a single, but different isomer. It is interesting to note that the mononitration of pentaalkoxytriphenylenes also produces a single, unexpected product that contrasts bromination. [13]

1. Experimental

2,3-Dimethoxytriphenylene **21a**.

4’,5’-dimethoxy-1,1’:2’’,1’’-terphenyl **19a** (1.40 g, 4.86 mmol) was stirred in DCM (150 ml) at room temperature. FeCl3 (3.94 g, 24 mmol) was slowly added and the mixture was stirred for 2 hours. The reaction mixture was then cooled (ice-salt bath) and methanol (100 ml) was added to the mixture with stirring. The solvents were evaporated and DCM was added to the residue. The organic phase was washed four times with water and extracted with DCM (3×150 ml). The solvents were evaporated and the residue was purified by column chromatography using DCM-petroleum ether (2:8) as eluent to give the product as a colourless solid obtained (1.19 g, 85%). Mp 168 oC; 1H NMR (400 MHz, CDCl3) δ= 8.67 – 8.60 (m, 2H), 8.50 (dd, 2H, J=2.0, 7.4), 7.99 (s, 2H), 7.67–7.54 (m, 4H), 4.11 (s, 6H, CH3); 13C NMR (100 MHz, CDCl3) δ = 149.58, 129.65, 129.33, 127.24, 126.48, 124.33, 123.59, 122.95, 104.63, 56.17.

2,3-Bis(hexyloxy)triphenylene **21b**.

A solution of 4’,5’-bis(hexyloxy)-1,1’:2’’,1’’-terphenyl **19b** (2.453 g, 5.696 mmol) in dichloromethane (125 mL) was stirred at room temperature. Iron (III) chloride (4.6198 g, 0.0284 mmol) was added and the reaction mixture was stirred for a further two hours. The reaction mixture was cooled to -10oC and methanol (50 mL) was added. The solvents were removed *in vacuo*, and the resulting crude residue dissolved in dichloromethane. This was then washed with water four times, the organics collected and dried over magnesium sulphate. The solvent was removed *in vacuo* and the crude product was loaded onto a silica gel column (pore size 40-63µ). The column was eluted using dichloromethane (10%) in petroleum ether, giving 2,3-bis(hexyloxy)triphenylene **21b** as a white solid (1.437 g, 59%). IR (thin film) ν 2926, 2855, 1613, 1185 cm-1; 1H NMR (400 MHz, CDCl3) δ = 8.57 (dd, 2H, J=1.7, 7.7Hz), 8.43 (dd, 2H,J=1.7, 7.7Hz), 7.95 (s, 2H), 7.53-7.56 (m, 4H), 4.18 (t, 4H, J=6.6Hz), 1.88 (pentet, 4H, J=6.7Hz), 1.57-1.30 (m,12H), 0.86 (t, J=7.0Hz, 6H); 13C NMR (100 MHz; CDCl3) δ = 150.02, 130.50, 129.54, 128.65, 126.14, 124.59, 123.53, 120.53, 106.39, 69.34, 31.64, 29.26, 25.80, 22.65, 14.05.

Dinitrotriphenylene **24**.

2,3,6,11-Tetrakis(hexyloxy)triphenylene **9** (2.00 g, 3.18 mmol) was crushed to a fine powder and dissolved in diethyl ether (100 mL) and acetic acid (30 mL). Nitric acid (3 mL) was added slowly and the reaction heated at reflux for 16 hours. After cooling, the reaction mixture was washed with water (2x100 mL) and sat. potassium carbonate solution (2x100 mL). The organics were collected, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was loaded onto a silica column and eluted with DCM: petroleum ether 3:10. The pure product **24** was obtained as a yellow oil (1.51 g, 66%). IR (thin film) ν 2932, 2860, 1532, 1525 cm-1; 1H-NMR (500 MHz, CDCl3) δ 8.47 (d, J = 9.2 Hz, 2H), 7.56 (s, 2H), 7.28 (d, J = 9.2 Hz, 2H), 4.19 (t, J = 6.4 Hz, 4H), 4.09 (t, J = 6.4 Hz, 4H), 1.94 - 1.78 (m, 8H), 1.54 - 1.47 (m, 8H), 1.40 - 1.33 (m, 16H), 0.94 - 0.90 (m, 6H) ppm; 13C NMR (126 MHz, CDCl3) δ 149.61, 149.46, 137.62, 125.06, 122.08, 121.26, 120.91, 112.06, 107.65, 69.87, 68.88, 31.67, 31.55, 29.05, 28.98, 25.76, 25.46, 22.67, 22.57, 14.03, 13.98 ppm; HRMS (ASAP (Solid)) *m/z* calculated for C42H58N2O8 [M+H]+: 719.4266; found: 719.4262.

Triphenylene diamine **25**.

2,7,10,11-Tetrakis(hexyloxy)-1,8-dinitrotriphenylene **24** (1.00 g, 1.391 mmol) and tin powder (2.31 g, 0.0195 mol) were stirred in acetic acid (100 mL), and the mixture heated at reflux for 2 hours. Upon completion, the hot solution was poured into water (300 mL) and extracted with dichloromethane (3x100 mL). The organics were collected, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was filtered through a pad of silica and used immediately (494 mg, 52%). 1H NMR (500 MHz, CDCl3) δ 8.82 (s, 2H), 7.82 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 4.42 (s, 4H), 4.11-4.13 (m, 8H), 1.94 – 1.85 (m, 8H), 1.58 – 1.49 (m, 8H), 1.42 – 1.34 (m, 16H), 0.94-0.95 (m, 12H) ppm.

Triphenylene Bisimide **26**.

2,7,10,11-Tetrakis(hexyloxy)triphenylene-1,8-diamine **25** (203 mg, 0.308 mmol) was stirred in chloroform (30 mL) with pyridine (0.348 mL, 341 mg, 4.315 mmol). Acetyl chloride (0.154 mL, 169 mg, 2.157 mmol) was added and the reaction mixture stirred for 16 hours. Upon completion, the reaction mixture was washed with sat. copper sulphate solution (2x50 mL), then water (2x50 mL) and extracted with dichloromethane. The organics were combined and dried over magnesium sulphate, before being concentrated *in vacuo*. The crude product was loaded onto a silica column and eluted with ethyl acetate: petroleum ether 1:5, and recrystallized from ethanol giving pale yellow crystals (102 mg, 40%) mp. 99-101oC; IR (thin film) ν 2933, 2860, 1713 cm-1; 1H-NMR (500 MHz, CDCl3) δ 8.51 (d, J = 9.3 Hz, 2H), 8.03 (d, J = 9.3 Hz, 2H), 7.24 (d, 2H), 4.10 (t, J = 6.4 Hz, 4H), 4.05 (t, J = 6.7 Hz, 4H), 2.17 (s, 12H), 1.90 – 1.77 (m, 8H), 1.54 – 1.43 (m, 8H), 1.40 – 1.32 (m, 16H), 0.92 (m, 12H) ppm; 13C NMR (126 MHz, CDCl3) δ 174.16, 153.15, 148.83, 128.52, 125.03, 124.74, 124.09, 123.86, 111.87, 109.14, 77.41, 77.16, 76.91, 69.14, 68.82, 31.73, 31.64, 29.42, 29.28, 26.08, 25.81, 25.77, 22.75, 22.73, 14.16, 14.16; HRMS (ASAP (Solid)) *m/z* calculated for C50H70N2O8 [M+H]+: 827.5205; found: 827.5209.

1. Conclusions

The chemistry of triphenylene-based systems has been expanded by two parallel developments – the controlled construction of triphenylene cores and their subsequent modification by electrophilic aromatic substitution (or related) reactions. George Gray was fascinated by the potential that the new synthetic breakthroughs could offer, and his enthusiasm for the field impacted on its development. We report here two further refinements to the chemistry – controlling the easy formation of 2,3-dialkoxytriphenylenes like **21**, and the unexpected regiochemistry observed following nitration of tetraalkoxytriphenylene **9**.

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List of Legends

Figure 1. The triphenylene core and the HATn series of discotic liquid crytsals.

Figure 2. Rigid triphenylene twins displaying nematic mesophases.

Scheme 1. Schematic representation of the approaches developed to assemble symmetrical and unsymmetrically substituted triphenylenes.

Scheme 2. Examples of the controlled construction of di- and tetra-alkoxytriphenylenes and their subsequent functionalization to give new families of discotic liquid crystals.

Scheme 3. Synthesis of 2,3-dialkoxytriphenylenes.

Scheme 4. Nitration of HAT6 *via* conventional electrophilic aromatic substitution, and chlorination using iodine monochloride.

Scheme 5. Nitration of tetrakis(hexyloxy)triphenylene and subsequent functional group interconversion to give crystalline diimide **26**.

Figure 1



Scheme 1



Scheme 2





Figure 2



Scheme 3



Scheme 4.



Scheme 5

