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To be cited as: *Chem. Eur. J.* 10.1002/chem.201701170

Link to VoR: http://dx.doi.org/10.1002/chem.201701170

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Straightforward Synthesis of 2- and 2,8-Substituted Tetracenes

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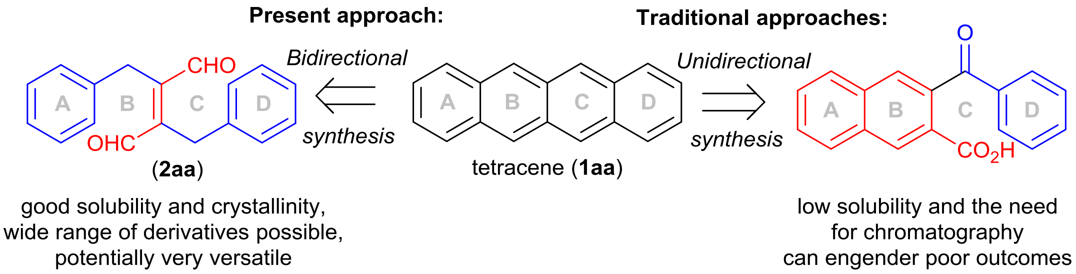
Abstract: A simple regiospecific route to otherwise problematic substituted tetracenes is described. The diverse cores (*E*)-1,2-$Ar^1CH_2(HOCH_2)C{=}C(CH_2OH)I$ (Ar^1 = Ph, 4-MePh, 4-MeOPh, 4-FPh) and (*E*)-1,2-$I(HOCH_2)C{=}C(CH_2OH)I$, accessed from ultra-low cost $HOCH_2C{\equiv}CCH_2OH$ at multi-gram scales, allow the synthesis of diol libraries (*E*)-1,2-$Ar^1CH_2(HOCH_2)C{=}C(CH_2OH)CH_2Ar^2$ (Ar^2 = Ph, 4-MePh, 4-*i*PrPh, 4-MeOPh, 4-FPh, 4-BrPh, 4-biphenyl, 4-styryl; 14 examples) by efficient Negishi coupling. Copper-catalysed aerobic oxidation cleanly provides dialdehydes (*E*)-1,2-$Ar^1CH_2(CHO)C{=}C(CHO)CH_2Ar^2$ which in many cases undergo titanium(IV) chloride induced double Bradsher closure providing a convenient method for the synthesis of regiochemically and analytically pure tetracenes (12 examples). The sequence is typically chromatography-free, scalable, efficient and technically simple to carry out.

Introduction

Of diverse utility in organic electronics[1] (including light emitting, transistor, sensor and solar cell applications) tetracene (**1aa**, Scheme 1), and its derivatives, must be synthesised[2] due to the lack of terrestrial sources.[3] This situation accounts for the 500-fold cost difference between anthracene and tetracene **1aa** (ca. 7 cents/mmol vs. €35/mmol).[4] We sought a route to **1aa**, and simple derivatives, which fulfilled the following characteristics: (i) minimised total step-count (ii) use of only low cost sustainable starting materials, (iii) diversity orientated intermediates facilitating the preparation of substituted tetracene libraries, (iv) simple (chromatography-free) work-up procedures providing analytically pure intermediates and final tetracenes, (v) applicability to gram scales without yield or purity degradation issues. While many elegant approaches to (substituted) tetracenes (**1**) are known[2] failures against one or more of the criteria (i)-(v) are unfortunately extremely commonplace. Traditional routes to tetracene derivatives typically involve *unidirectional synthesis* from *ortho* substituted phenylene units wherein only one ring is formed at a time (e.g. C-ring closure in the right of Scheme 1). The nice commercial (3M) process to 2-chlorotetracene of Gerlach is a good example of such a disconnection.[5] We thought to use *bidirection synthesis*, a powerful tool in natural product preparation,[6] but which is rarely used in accessing tetracenes[7] or indeed polyaromatics[8] in general.



Scheme 1. The approach herein to tetracenes (**1**) using bidirectional[6] closure (B,C-ring formation) of highly soluble and crystalline *bis*-aldehydes (**2**) vs. an exemplary unidirectional synthesis. Adding substituents to the A/D phenyl groups allows access to acene derivatives.

The proposal on the left of Scheme 1 requires Bradsher[9] (hydroxyalklation) closure of both aldehydes in **2** directly forming the B and C rings of tetracenes **1** in a single pot. Such two-directional strategies have no exact precedent in tetracene synthesis as far as we can tell. Naphthalene formation from simple *cis*-1,2-substituted alkene(CHO)(CH_2Ph) fragments (the closest analogue of the required B-ring formation in Scheme 1) is described in a handful of cases.[10] Less than a dozen papers describe 'one-directional' H^+/Lewis acid closure of phenylene(CHO)(CH_2Ph) units (the reaction most analogous to the required C-ring closure to tetracene). Anthracenes[11] and benzo[*g*](iso)quinolones,[12] a *bis*-naphthothieno[2,3-d] thiophene,[8a] a trinaphthylene[8b] and one very recent tetracene[8c] have been prepared this way. Contemporary (2016-17) alternatives have highlighted gold[13] and Fe(III)[14] catalysed two-directional syntheses to dihydrotetracenes and various polyaromatics, respectively. However, preparation of some cyclisation precursors can be step/chromatographically intensive in such approaches. Cyclisation promotors for tetracene formation in particular need careful selection: H^+ is commonly used to instigate Bradsher reactions,[8,9] but such conditions can also readily oxidise the tetracene products to unstable radical cations (that are known to subsequently decompose to complex mixtures).[15] The use of Lewis acid cyclisation is preferred, but in some cases even these are overly oxidising towards tetracenes.[16] However, if such issues are overcome core **2** is an attractive precursor for tetracene library synthesis as no post-cyclisation *C*-oxidation state manipulation is required (c.f. quinoid and dihydrotetracene routes to tetracenes[2]), water being formally the only by-product produced in the Bradsher aromatisation.

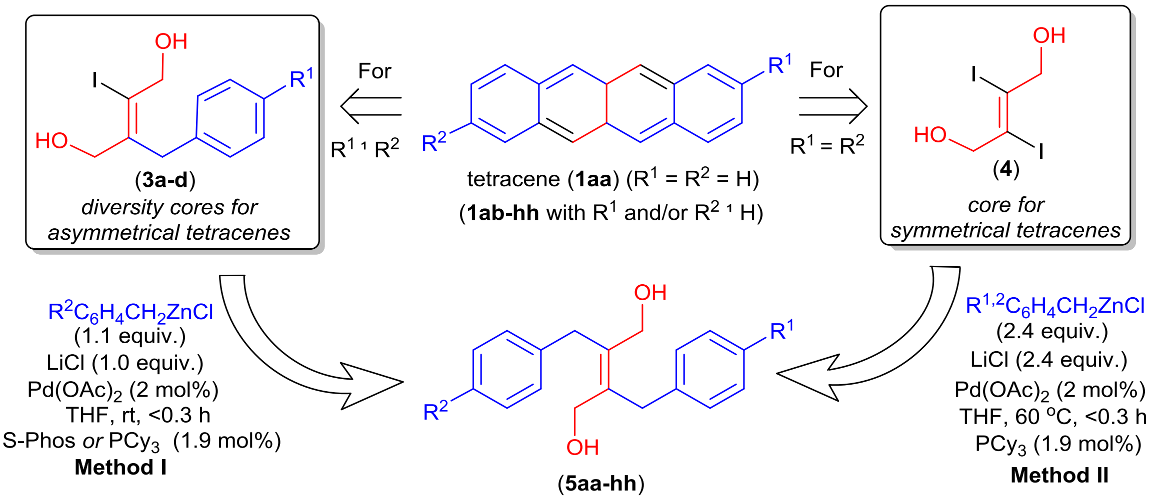
Results and Discussion

We proposed that all of the carbons in our tetracene synthesis should arise from low cost and sustainable 2-butyne-1,4-diol (4 cents/g)[4] and benzyl chloride (3 cents/g)[4] or its simple derivatives via the diversity orientated iodides **3-4** (Table 1). Copper-catalysed ($CuBr{\cdot}SMe_2$, 2 mol-%) direct addition of 4-(R^1)$C_6H_4CH_2MgCl$ to $HOCH_2C{\equiv}CCH_2OH$ proceeds, under our modified literature conditions, to the expected (-OMgCl directed[17]) (*E*)-carbomagnesiation intermediate which smoothly intercepts iodine providing the new diversity cores **3a-d** (see Supporting Information). Acceptable to good (58-72%) yields, on 10 g scales, are attained by direct crystallisation of the crude reaction products. In the case of **3c**, removal of a Wurtz by-product is necessary prior to recrystallization but this too is straight forward, even at multi-gram levels. Increasing the carbomagnesiation reaction temperature to 50-55 °C is the key to attaining high conversion in these cabocuprations of lower reactivity benzylic Grignard reagents.[17] Equally conveniently, **4** directly precipitates as an off-white solid from a simple reaction of 2-butyne-

1,4-diol with iodine in $CHCl_3$ on >10 g scales (90% yield), using our modified conditions.[18] The simplicity of the preparations of **3-4** has encouraged us regarding their commercial availability.[19]

Iodides **3-4** are potent precursors for straightforward Negishi-type couplings providing **5** efficiently and quickly (Table 1). Previously, slow addition techniques and specialist ligands have been necessary to avoid competitive deprotonation in such unprotected alcohol substrates.[20] However, this is not the case for **5** and a wide range of asymmetric diols can be realised in excellent yields (85-99%) using a typical S-Phos biaryl ligand.[20] Simple non-proprietary tricyclohexylphosphine (PCy_3) also provides equivalent yields (in all cases tested, Method I). These catalytic Negishi couplings show very strong ligand inhibition at L/Pd ratios of >1 but use of a slight deficiency of phosphine in the coupling prevents this becoming an issue. Isolation of the diols **5** is facilitated by their low solubility in Et_2O, typically trituration in this solvent provides off-white solids (>98% pure) that can be used directly in subsequent transformations. Acetonitrile can be used to similar effect. Finally, the diols **5** are often highly crystalline and frequently attained as glinting colourless analytically pure needles from simple hot MeOH:EtOAc mixtures. By appropriate combination of **3** and benzyl zinc reagent the symmetric diols may also be readily achieved (i.e. **5aa** is attained from **3a** and $PhCH_2ZnCl$ in 87% yield). Alternatively, the symmetrical diols can also be attained from **4** and slight excesses of the appropriate benzylic zinc reagent (Method II). While the scope of this symmetrical coupling is not quite as wide as that from use of **3a-d** (e.g. preparation of **5bb** by Method II provides only 56% vs. 93% via method I) it does allow routine access to the symmetrical diols quickly. For example, **5aa** could be prepared on a >10 g scale by such approaches within a day.

Table 1. Diversity orientated synthesis of the diol tetracene precursors **5**.[a]



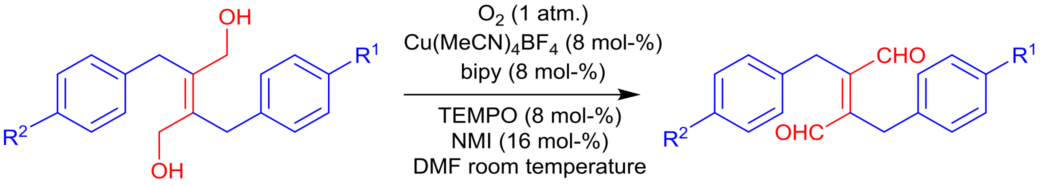
Iodide used	Method	R^1	R^2	Diol	**5** (%)	Recrystallisation from^b	m.p. (°C)
3a	I	H	H	**5aa**	87	1:1 MeOH/AcOEt	157-158
4	II	H	H	**5aa**	62-72	-	-
3a	I	H	Me	**5ab**	84	1:1 MeOH/AcOEt	150-151
3a	I	H	OMe	**5ac**	91	3:1 EtOAc/MeOH	131-132
3a	I	H	F	**5ad**	82	1:1 MeOH/AcOEt	139-140
3a	I	H	Ph	**5ae**	99	1:1 MeOH/AcOEt	154-155
3b	I	Me	Me	**5bb**	93	1:1 MeOH/AcOEt	180-181
4	II	Me	Me	**5bb**	56	-	-
3b	I	Me	*i*Pr	**5bf**	87	1:1 MeOH/AcOEt	155-156

3b	I	Me	vinyl	**5bg**	96	*i*PrOH, -20 °C	161-164
3b	I	Me	Br	**5bh**	92	1:1 MeOH/AcOEt	153-154
3c	I	OMe	Me	**5cb**	93	3:1 EtOAc/MeOH	131-132
3c	I	OMe	OMe	**5cc**	85	MeCN, -20 °C	145-146
3c	I	OMe	F	**5cd**	85	3:1 EtOAc/MeOH, -20 °C	119-120
3d	I	F	F	**5dd**	82	MeCN, -20 °C	129-130
4	II	Br	Br	**5hh**	65	MeCN, -20 °C	139-140

[a] Typically reactions were carried out on ca. 6 mmol scales in THF (25 mL) over 15-20 min. Recrystallisation from refluxing solvent on cooling to 4 °C unless indicated otherwise.

Oxidation of diols **5** to the aldehydes **2** is necessary prior to tetracene cyclisation (Scheme 1). This is sustainably attained by the aerobic Cu^I/TEMPO-based catalysts (Table 2), optimised by Stahl;[21] environmentally poorer oxidants (e.g. MnO_2, Swern) performed less well (see Supporting Information). The slightly modified oxidation procedure used herein shows useful functional group tolerance: both C-Br and styryl functions are preserved even though oxidation procedure is radical driven.[21] Conveniently these oxidations are self-indicating: initiation of the catalyst commensurate with the immediate appearance of a dark orange-brown colour which becomes emerald green on completion of the oxidation (0.3-1 h). After isolation and drying under vacuum the dials **2** are attained as bright yellow solids in high yield and >98% purity allowing their direct use for immediate tetracene synthesis without any further purification. However, all are also easily recrystallized as glinting yellow flakes from *i*PrOH or *i*PrOH:EtOAc mixtures. Oxidation of the diols **5** at a gram scale is straightforward and further scale-up not an issue: e.g. **2aa** could be attained on a 4 g level without the need for any chromatographic separations. Minor modification of the reaction temperature (to 40 °C) is necessary for diol **5ae** to ensure full solubility and completion of reaction.

Table 2. Copper(I)-catalysed oxidation of diols **5** to aldehydes **2**.[a]



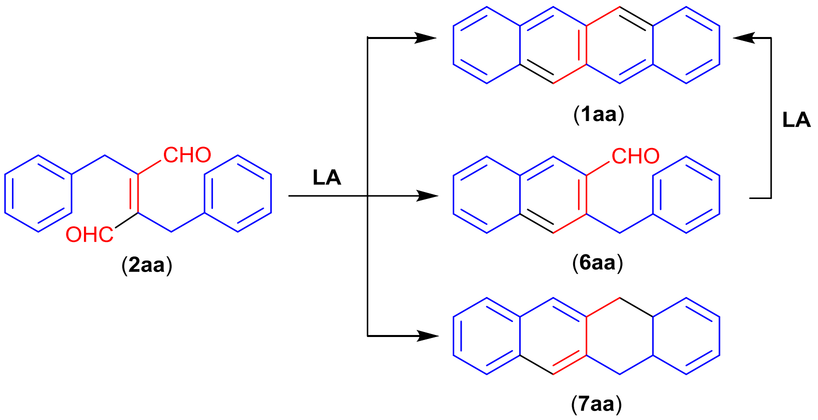
(**5a-m**) (**2a-m**)

5 used	R^1	R^2	**2** (%)	**5** used	R^1	R^2	**2** (%)
5aa	H	H	>99	**5bg**	Me	vinyl	87
5ab	H	Me	87	**5bh**	Me	Br	98
5ac	H	OMe	88	**5cb**	OMe	Me	95
5ad	H	F	92	**5cc**	OMe	OMe	>99
5ae	H	Ph[b]	96	**5cd**	OMe	F	85
5bb	Me	Me	93	**5dd**	F	F	89
5bf	Me	*i*Pr	89	**5hh**	Br	Br	93

[a] Typically reactions were carried out on ca. 3 mmol scales in DMF (18 mL) over 1 h.
[b] Reaction at 40 °C.

Preliminary small scale Bradsher closure trials of dialdehyde **2aa** with a library of 14 Lewis acids (Scheme 2, **LA**, see also Supporting Information) revealed that only $In(OTf)_3$, $BF_3{\cdot}OEt_2$ and $TiCl_4$

were active towards tetracene (**1aa**) formation (Scheme 2). Therefore, these three promotors were all examined in detail. For In(OTf)$_3$ (at 0.6 equivalents) significant conversion to the desired tetracene **1aa** could only be achieved by prolonged heating at 83-115 °C (Supporting Information); the rate was insufficient for lower catalyst loadings to be viable at practical scales (necessary for viable use of such a poorly sustainable **LA** promotor). Two additional products: **6aa**[22] and **7aa**[13,23] (Scheme 2) could also be detected in these indium-promoted closures by comparison with their published ^{1}H NMR data (independent samples of **6aa** can be prepared by much less efficient alternate chemistry[22]). Monitoring the reaction by ^{1}H NMR spectroscopy also confirmed that **6aa** is a genuine 'half closure' intermediate on route to tetracene **1aa**.

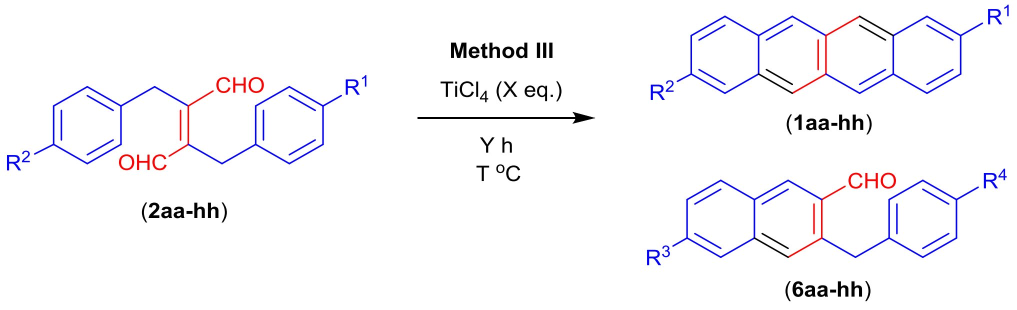


Scheme 2. An intermediate (**6aa**) and by-product (**7aa**) in Bradsher closures of aldehyde **2aa** to tetracene (**1aa**).

Stoichiometric BF$_3$·OEt$_2$ is much more attractive reagent for tetracene formation due to its low cost. With two equivalents of BF$_3$·OEt$_2$ at scales below 1 mmol (in **2aa**), good yields (>80%) of tetracene **1aa** are attained at 1,2-dichloroethane reflux (83 °C) conditions within 5 h. Unfortunately, at larger scales (especially >3 mmol) these reactions become capricious, progressively less clean (with increasing scale) and result ultimately in negligible or no yields of **1aa**. The water by-product of the Bradsher cyclisation is the cause of these issues. Efficiently minimised in small scale reaction mixtures by 1,2-dichloroethane azeotrope formation (b.p. 70.5 °C), in larger scale reactions water promoted H[HOBF$_3$][24] formation competes leading to acid-induced oxidation of **1aa**[15,24] providing **7aa** (among many other radical cation derived by-products). Control studies support this idea: deliberate addition of water (2 equiv.) to the reaction mixture at the outset, prior to BF$_3$·OEt$_2$ (2.0 equiv.) addition and subsequent reflux, leads to catastrophic reduction in the **1aa** yield regardless of the scale of the reaction. Deployment of 4Å molecular sieves in the reaction headspace allows production of **1aa** at a gram scale, but initiation of the cyclisation then becomes slow and equally capricious. Kinetic study of the BF$_3$·OEt$_2$ promoted cyclisation of **2aa** (0.28 M) provides insights into these behaviours (see Supporting Information). Formation of **1aa** (and disappearance of **6aa**) follow an autocatalytic rate law over 4 h at 63 °C. Dial **2aa** is rapidly converted to **6aa** under these conditions, and fitting standard autocatalysis rate law forms[25] to the disappearance of **6aa** provides k_1 ~0 min^{-1} and k_2 = 0.3 M^{-1} min^{-1} where k_1 and k_2 are respectively estimates of the background and autocatalytic behaviour (see Supporting Information). This strong autocatalysis is the root cause of the reliability issues in larger scale preparations of **1aa** using BF$_3$·OEt$_2$. Controlling the reactive H[HOBF$_3$] concentration simply becomes impractical at any significant scale in **2aa**. By using only one equivalent of BF$_3$·OEt$_2$ high yields of **6aa** could be obtained at room temperature, again confirming it as an intermediate en route to **1aa**. In 2015 the syntheses of three tetracenes using a $BF_3\cdot OEt_2$ promoted (unidirectional) Bradsher process were disclosed.[11c] The colours described for these acenes (colourless to pale green) are not in accord with tetracene formation (which are all typically all brilliant orange). We believe the potential for decomposition effects during the reaction/workup of these reactions similar to the effects observed herein cannot be excluded.

In an attempt to overcome the reproducibility issues associated with BF_3-H_2O autocatalysis we also screened the little used, low cost, $TiCl_4$ Bradsher conditions of Tius (Method III, Table 3).[10c] To our great delight quench (of the most unpromising brown-green reaction mixtures) with 1:1 methanol:acetone resulted in spectacular orange precipitates of **1aa**. Despite the small particle size of the **1aa** produced, very easy filtration is facilitated by use of Whatman glass microfiber filter paper (GF/A which is designed to collect particles sized down to 1.6 μm efficiently). The $TiCl_4$ approach proved rather general for cyclisation of aldehydes **2**, subject to the usual electronic effects on electrophilic aromatic substitution (Table 3). Partial closure products **6** could often be seen from the filtrates, especially when the donor/acceptor properties of R^1/R^2 were different. The initially precipitated tetracenes **1** are attained in purities (>95%) sufficient for immediate subsequent synthetic/materials application uses. Simple one-step sublimation (200-230 ºC, 0.1-0.2 mbar, 1 h) easily provides analytically pure materials as brilliant orange mircocrystals. For electronically deactivated dialdehydes (e.g. **2ad**) the use of larger excesses of $TiCl_4$ (4 equiv.) under neat reaction conditions and longer reaction times (typically 2 days) are required and low to modest yields are attained with these general conditions. Attempts to force closure of the species **6** led to variable outcomes (see Supporting Information). For example, dosing **2dd** with $TiCl_4$ aliquots over 4 days led to up to 40% conversion to **1dd** in some runs but mostly decomposition in others. Bradsher cyclisations are known to be subject to the normal electronic deactivation restrictions of Friedel-Crafts chemistry and thus the procedures here are best used on electron-rich systems. Activated **2bg** was extensively cross-linked on reaction with even one equivalent $TiCl_4$ at room temperature providing an insoluble orange macromolecular material. Repeating this synthesis at -78 to -40 ºC provides oligomeric **1+6bg**$_n$ with n ~ 7-8 through controlled polymerisation of the vinyl side chain and mixed mono and di-Bradsher closure. For both the oligo and macromolecular **1+6bg** characteristic tetracene spectroscopic bands can be identified in their UV-vis and IR spectra. Interestingly the monomeric tetracenes **1** all show intense refractive index matching in diamond anvil ATR-IR instruments. The resulting anomalous dispersion leads to the observation of apparent negative peaks around the diamond absorbance range (2100-2000 cm^{-1}) which are a useful quick diagnostic for **1** (even in mixtures), especially if a characteristic peak at ~905 cm^{-1} is also present. In line with this suggestion, no pseudo emission peaks are seen using Ge-crystal ATR instruments.

Table 3. Method III: titanium(IV) chloride induced Bradsher cyclisations.[a]



2 used	R^1	R^2	X (eq.)	Y (h), T (ºC)	**1** (%)	Lit. **1** %[b]	Ref.	**6** (%)	R^3	R^4
2aa	H	H	2	3 (40)	72	51 (3)	26	-	-	-

2aa	H	H	2	2 (40)	40	-	-	**6aa** (50)	H	H
2ab	H	Me	2	3 (40)	68	4 (1)	27	**-**	-	-
2ab	H	Me	2	1 (22)	27	-	-	**6ab** (57)	Me	H
2ac	H	OMe	2	3 (40)	56[c]	88 (4)	28	-	-	-
2ad	H	F	4	60 (22)	9	56 (3)	29	**6ad** (37)	H	F
2ae	H	Ph	2	3 (40)	71	-	30	-	-	-
2bb	Me	Me	2	3 (40)	86	low (2)	31			
2bf	Me	*i*Pr	2	3 (40)	86	-	-			
2bg	Me	vinyl	2	Note [d]	62	-	-	**1+6bg**$_n$ (65-89)	Oli[e]	Oli[e]
2bh	Me	Br	4	60 (22)	4	-	-	**6bh** (45)	Me	Br
2cb	OMe	Me	2	3 (40)	81	-	-	-	-	-
2cc	OMe	OMe	2	3 (40)	86	-	-	-	-	-
2cd	OMe	F	4	60 (22)	8	-	-	**6cd** (39)	OMe	F
2dd	F	F	4	60 (22)	Var. [f]	-	-	**6dd** (63)		
2hh	Br	Br	4	60 (22)	-	31 (3)	32	**6hh** (54)	Br	Br

[a] Typically reactions carried out on 1.5 mmol scales in 1,2-dichloroethane (10 mL); TiCl$_4$ added at 0 °C, and the mixture stirred at the required temperature. Electronically deactivated substrates (**ad**, **cd**, **dd**, **hh**) were run in neat TiCl$_4$ (see Supporting Information).

[b] The highest/best analogous literature (substituted)tetracene procedure we could identify and (in parentheses) the number of steps needed to prepare the required precursor from commercial (<0.1€ mmol^{-1}) materials.

[c] Higher solubility limits precipitated yield.

[d] Reactions carried out at 22 °C afford a low solubility high polymer containing both tetracene and aldehyde groups. Reaction at -78 to -40 °C leads to a soluble oligomer.

[e] 'Oli' indicates product is a (CHCH$_2$)$_n$ oligomer with n ~ 7-8 generated by polymerisation of the vinyl sidechain providing a telechelic oligomer with both tetracene and aldehyde pendant groups present (see Supporting Information).

[f] Low (<5%) yields were attained under standard conditions, by adding 1,2-dichloroethane co-solvent and extending the reaction to >3 days up to 40% yields were sometimes attained together with intractable decomposition products (see Supporting Information).

Conclusions

The synthetic sequence to **1** from the iodides **3-4** constitutes an effective and practical route for the formation of 2- and 2,8-substituted tetracenes in high analytical purities atypical to most other literature approaches. All of the tetracenes **1** prepared showed the expected spectroscopic properties and have solubilities in CH$_2$Cl$_2$ ranging from ca. 10^{-6} M (**2bh**) to ~10^{-3} M (**2ac** and fluorine containing tetracenes). The lower solubilities, in part, account for the success of our direct precipitation work-up strategy. From Table 3 it is clear that the approach described herein is complimentary, and in the case of electron-rich substituted tetracenes, advantageous to existing methodology. In particular, the ability to prepare tetracene libraries of various substituents at significant scales quickly and without the use of chromatography is attractive for their subsequent use in materials science at larger preparative scales. The electronic properties of the tetracenes attained are also in line with predictions. For example, 2-methyltetracene (**2ba**) shows an measured E$_g$(opt) of 2.50 eV which is close to the calculated HOMO-LUMO gap by time dependant DFT of 2.76 eV [CAMB3LY-6-31G(d,p) level of theory] and the accepted value for the parent **1aa** (2.61 eV) [Eg(calc) is typically greater than Eg(opt), see Supporting Information]. For the tetracenes prepared herein we could control E$_g$(opt) in the range 2.54-

2.43 eV by substituent effects. Such ability to easily and systematically vary the HOMO and LUMO energies of tetracenes are central to their use in organic electronic applications and the approach herein simplifies the synthetic effort required to enact the required substituents at useful scales in many cases.

Experimental

Full details for the preparation of **1-7** and their properties are given in the Supporting Information.

Acknowledgments

This work was initiated under funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 308768. One of us (JR) is grateful to European Thermodynamics Ltd and the Engineering Physical Sciences Research Council (EPSRC) for provision of a studentship. SW, LB and JR thank EPSRC's National Service for Computational Chemistry (NSCCS) for computational facilities until its closure in 2017. MA thanks the Swiss-European Mobility Programme (SEMP) and is grateful to Prof Steve Howdle and Ms Liv Monaghan for advice and help with GPC analyses. MRG is grateful for the award of an Appalachian College Association Fellowship for sabbatical leave support from Berea College, Kentucky, USA. We are indebted to Dr Callum Welsh (University of Nottingham) and Prof Jens Pflaum (Universität Würzburg) for helpful discussions on refractive index matching and anomalous dispersion effects in diamond anvil ATR-IR spectroscopic studies of tetracenes. We thank Dr Magdalena Foreiter for sample collaboration with Key Organics Ltd and Nottingham Research Chemicals.

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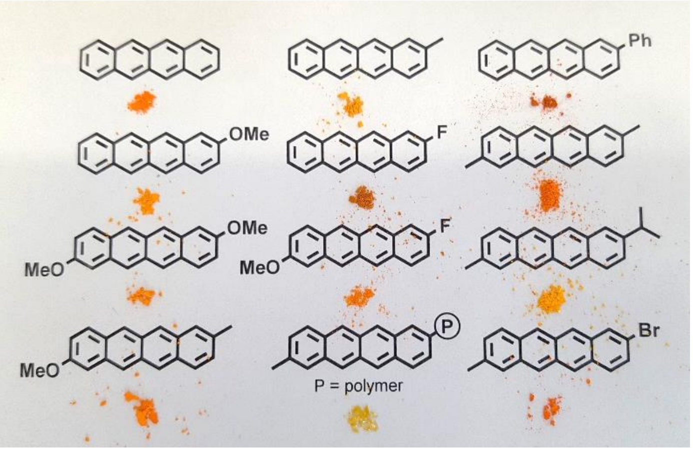

A simple procedure for the preparation of substituted tetracenes from low cost $ArCH_2Cl$ and $HOCH_2C\equiv CCH_2OH$.

Keywords:

Arenes • Aldehydes • Aromaticity • C-C coupling • Acenes • Bradsher cyclisation • Efficient