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Brønsted- and Lewis acid-catalyzed cyclization giving rise to substituted anthracenes and acridines†

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Abstract—A versatile acid-catalyzed method for the preparation of symmetrically and unsymmetrically substituted 9,10-diphenylanthracenes is explored. Diveratrylmethanes are prepared and converted into 10-phenylanthracene-9-carbaldehydes by Lewis acid catalysis and into 9-phenylacridines by reduction.

The acid-catalyzed condensation of veratrole (1,2-dimethoxybenzene) and formaldehyde leads to cyclotriveratrylene, an important building block in supramolecular chemistry.[1,2] On the other hand, with different aldehydes and veratrole, only the 9,10-disubstituted anthracenes are obtained.[3–5] Most of the work described deals with aliphatic aldehydes, with only one example referring to the synthesis of 9,10-diphenyl-2,3,6,7-tetramethoxyanthracene from veratrole and benzaldehyde.[2] We wanted to explore this reaction, as a general strategy towards 9,10-diarylanthracenes. A well known strategy for the preparation of 9,10-diarylanthracenes is a two-step procedure from anthraquinones, involving addition of a Grignard reagent or an aryllithium and reduction of the resulting diols.[6,7] The scope of this protocol was recently widened by the introduction of a new reducing agent by our group.[6] Obviously, metal-catalyzed couplings between 9,10-dihaloanthracenes and arylboronic acids are possible as well.[8] However, the direct condensation of an aromatic aldehyde with veratrole presented in this paper, allows the preparation of a number of these derivatives in one single and highly convenient step.

Firstly, we reinvestigated the reaction of veratrole **1** and benzaldehyde **2a** in a 1:2 ratio (Scheme 1). The literature[5] reaction conditions (84% sulfuric acid, 5°C) appeared to be optimal and other reaction conditions (lower or higher concentrations of sulfuric acid, glacial acetic acid) did not improve the yield of **3a**. This is typically around 40% which is also true for the synthesis of **3b–i** from substituted benzaldehydes **2b–i**. An advantage of this synthesis is that all anthracenes are substituted with four methoxy groups. This prevents association of the anthracenes and enhances their solubility. Anthracenes bearing aryl groups with 2′,6′-disubstitution at the 9- and 10-positions are less easily prepared: the yield for the preparation of **3b** is only 25%. However, we consider this compound to be of interest as we propose that such a substitution will protect the anthracene from oxidation or fluorescence quenching.

Polycyclic aromatic aldehydes, including pyrene-1-carboxaldehyde, 1- and 2-naphthaldehyde did not yield anthracenes and only starting material was recovered from the reaction mixture. The same was observed when heterocyclic aldehydes (thiophene-2-carboxaldehyde, 4-pyridinecarboxaldehyde, 4,6-dichloropyrimidine-5-carboxaldehyde) were used.

When the ratio of veratrole:benzaldehyde is changed from 1:2 to 3:1, one obtains in high yield the [2+1] adduct **4a**. This protocol can again be applied to a number of substituted benzaldehydes **2b–f,j**, affording the diveratrylmethanes **4b–f,j** in 60–80% yield.[9] Reaction of heterocyclic or polyaromatic aldehydes under these conditions again failed. It can be assumed that the diveratrylmethanes of type **4** are intermediates in the reactions with an excess of the aldehyde, leading to anthracenes **3a–i**. To test this, the adduct **4c** was combined with benzaldehyde (ratio 1:1.2). As we hoped, the main product (40% yield) was the unsymmetrically substituted anthracene **5c**.[10] On the other hand, a small amount of the symmetrical anthracene **3c** was also formed. The same observation was made for the reac-

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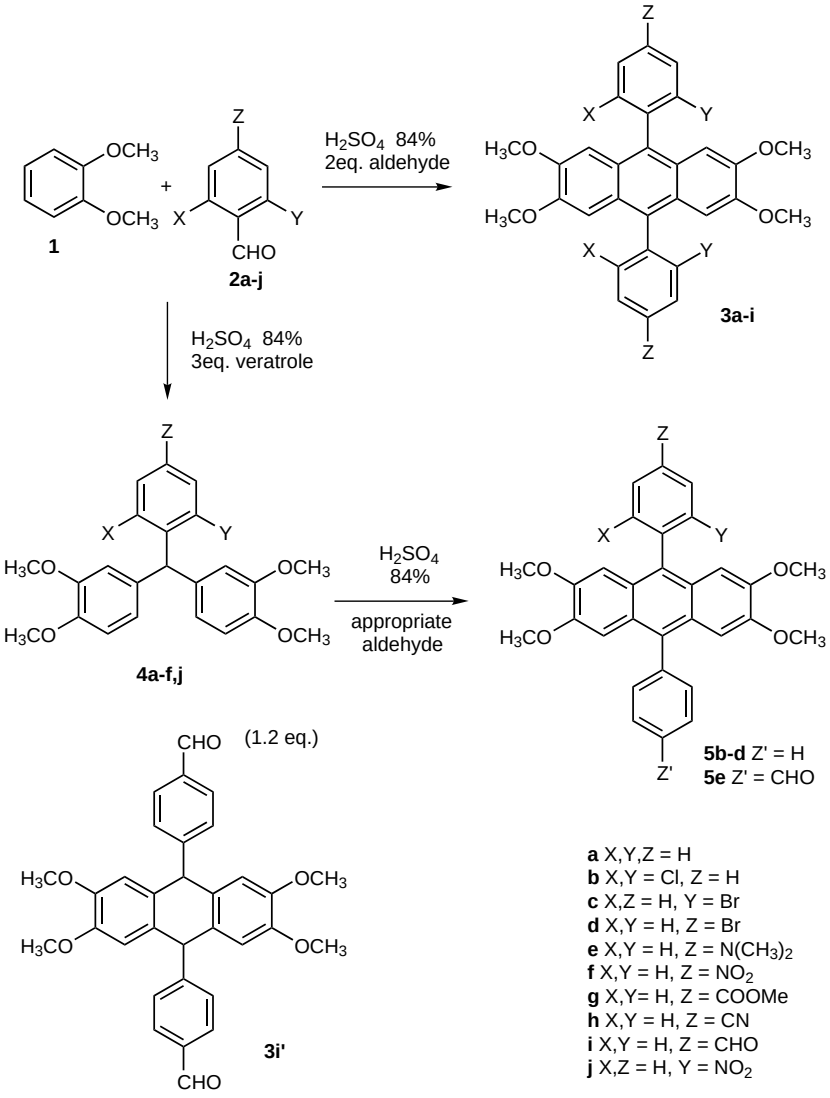
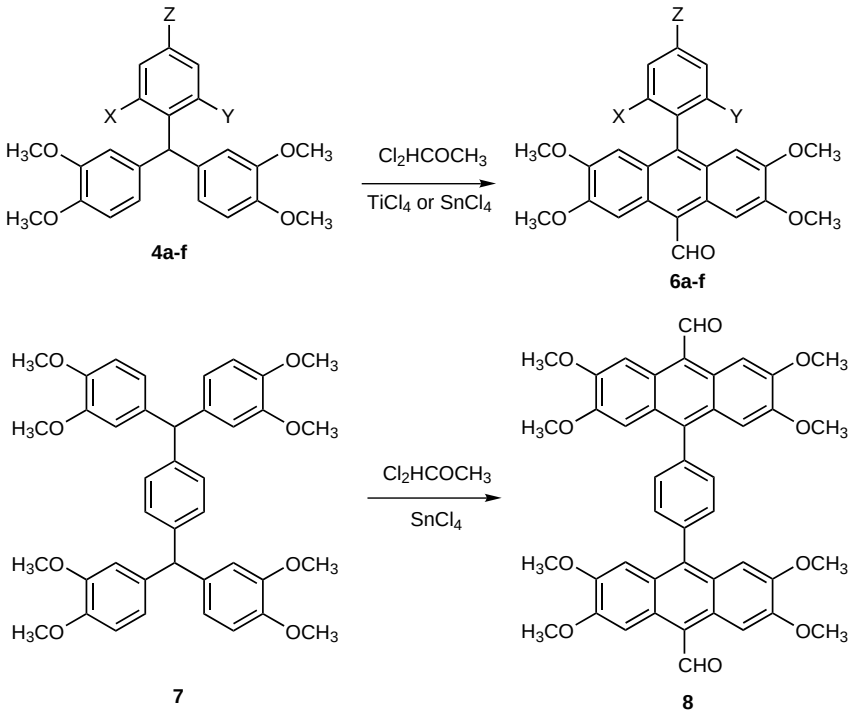


Scheme 1.

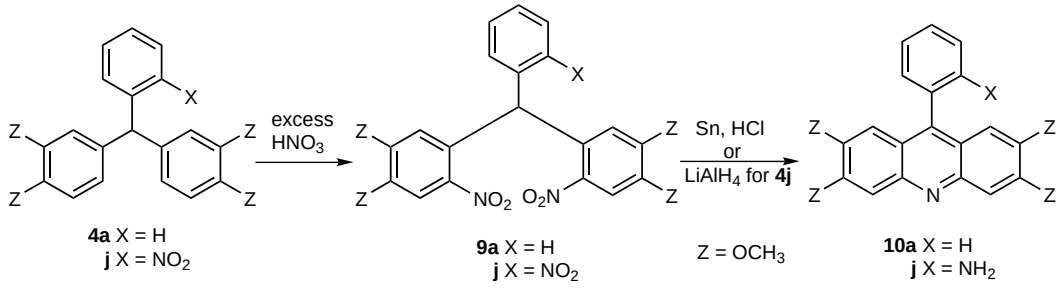
tion of **4d** with benzaldehyde. This proved that the condensation of **1** with **2c** and **2d** to **4c** and **4d**, respectively, is at least partially reversible under the reaction conditions. Adducts **4b**,**e** are less readily cleaved in acidic medium, and no exchange products are formed. This opens the possibility to obtain unsymmetrical anthracenes, e.g. **5e**, of potential use for non-linear optical (NLO) applications by sequential combination of veratrole with benzaldehydes having electron withdrawing and electron donating groups. Direct mixed condensation of equimolar amounts of **2e** and **2i** with veratrole yielded only **3i** and the proposed intermediate dihydroderivative **3i′**. Presumably, the presence of the electron rich dimethylaminobenzaldehyde prevents the expected oxidation of **3i′** to a certain extent.

As an alternative to obtain unsymmetrical diarylanthracenes of type **5**, we considered the Friedel–Crafts acylation of diveratrylmethane **4a**. With benzoyl chloride the intermediate benzophenone was expected to undergo a Bradsher reaction to afford the corresponding anthracene. Unfortunately, only starting material was recovered. The same result was obtained when we used the Vilsmeier formylation. Ring closure did occur with adducts **4a**–**f** and dichloromethyl methyl ether in the presence of $TiCl_4$ in dry dichloromethane[11] giving rise to 10-arylanthracene-9-carboxaldehydes **6a**–**f** in 30–80% yield (Scheme 2).[12] In the literature, these conditions have been applied to obtain anthracenes from less electron rich substrates. In our case, the yield could be improved to a reliable 70–90% when the softer $SnCl_4$ was used as the Lewis acid. Again, aldehyde **6e** with electron donating substituents is of potential use for the synthesis of NLO materials. Furthermore, we applied this synthetic method to prepare molecules with two anthracene moieties. Tetrakis(veratryl) adduct **7** was obtained from terephthaldehyde **2i** and a tenfold excess of **1**. Upon treatment with $SnCl_4/CHCl_2OCH_3$ this compound yielded the poorly soluble dialdehyde **8**.

Finally, we found that the diveratrylmethanes **4** were useful for the synthesis of 9-phenyl acridines. Therefore, diveratrylmethanes **4a** and **4j** were first nitrated using an excess of concentrated nitric acid, yielding the dini-



Scheme 2.



Scheme 3.

troderivatives **9a** and **9j** (70–90%) (Scheme 3). These compounds could then be ring-closed by reduction with tin in hydrochloric acid (36%) resulting in the formation of the acridines **10a** and **10j** (50–60%).[13] Obviously, in the case of substrate **9j**, this treatment resulted in the concomitant reduction of the 2′-nitro substituent. No formation of an isomeric 9-(3,4-dimethoxyphenyl)-2,3-dimethoxyacridine was observed. For derivative **9a**, $LiAlH_4$ in dry THF, gave a slightly higher yield (65%) of the desired 9-phenylacridine **10a**.

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9. General procedure for the preparation of compounds **4a**–**f**,**j**. A solution of veratrole (30 mmol, 3 equiv.) and the appropriate aldehyde (10 mmol, 1 equiv.) in dichloromethane (5 mL) was added dropwise to 84% sulfuric acid (10 mL) while the temperature was kept between 0 and

5°C. After the addition, the suspension was stirred for 1 h at room temperature. The reaction was quenched with water and neutralized by ammonia. After extraction with dichloromethane, the solvent was stripped off in vacuo and the product was purified chromatographically or by crystallization. Compound **4d** was obtained using the standard procedure. The crude product was purified by crystallization from methanol, affording **4d** in 70% yield; mp 136°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40 (2H, d, $J=8.4$ Hz, 3,5-H phenyl), 6.98 (2H, d, $J=8.4$ Hz, 2,6-H phenyl), 6.78 (2H, d, $J=8.3$ Hz, 4-H veratryl), 6.63 (2H, s, 1-H veratryl), 6.53 (2H, dd, $J=8.4$ Hz, 5-H veratryl), 5.38 (1H, s, Ar_3CH), 3.86 (6H, s, OCH_3), 3.76 (6H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 148.9, 147.7, 143.4, 136.0, 131.3, 131.0, 121.3, 120.1, 112.7, 111.0, 55.9, 55.8, 55.3; MS (EI) m/z 444 (M^+).

10. General procedure for the preparation of compounds **5b–e**. A solution of **4b–e** (10 mmol, 1 equiv.) and the appropriate aldehyde (12 mmol, 1.2 equiv.) in dichloromethane (5 mL) was added dropwise to 84% sulfuric acid (10 mL) while the temperature was kept between 0 and 5°C. After the addition, the suspension was further stirred for 1 h at room temperature. The reaction was quenched with water and neutralized by ammonia. After extraction with dichloromethane, the solvent was evaporated in vacuo and the product was purified chromatographically or by crystallization. Compound **5c** was prepared using the standard procedure. The crude reaction mixture was purified chromatographically eluting on silica gel with dichloromethane, affording **5c** in 40% yield; mp 243°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.88 (1H, d, $J=7.7$ Hz, 3-H phenyl), 7.50 (8H, m, 4-6-H phenyl, 2-6-H phenyl′), 6.84 (2H, s, 4,5-H anthracene), 6.60 (2H, s, 1,8-H anthracene), 3.74 (6H, s, OCH_3), 3.73 (6H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 149.7, 149.3, 140.9, 140.1, 134.1, 135.5, 133.4, 132.0, 131.4, 129.8, 129.1, 128.2, 127.9, 126.2, 126.2, 125.8, 104.6, 104.4, 103.7, 55.9; MS (E) m/z 530 (M^+). Anal. calcd: C, 68.06; H, 4.76. Found: C, 67.78; H, 4.94%.

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12. General procedure for the preparation of compounds **6a–f**. To a solution of **4a–f** (1 equiv.) in dry dichloromethane (25 mL) was added dichloromethyl methyl ether (5 equiv.) and $TiCl_4$ (4 equiv.) or $SnCl_4$ (4 equiv.) at room temperature. After stirring overnight, more dichloromethane was added (50 mL) and the solution was washed with water (3×100 mL). After evaporation of the solvent, the crude product was purified chromatographically. Compound **6d** was prepared according to the standard procedure. The crude product was purified chromatographically eluting on silica gel with dichloromethane, affording **6d** in 83% yield (when $TiCl_4$ was used) or 93% yield (when $SnCl_4$ was used); mp 230–232°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.42 (1H, s, CHO), 8.43 (2H, s, 4,5-H anthracene), 7.76 (2H, d, $J=8.4$ Hz, 3,5-H phenyl), 7.28 (2H, d, $J=8.4$ Hz, 2,6-H phenyl), 6.60 (2H, s, 1,8-H anthracene), 4.11 (6H, s, OCH_3), 3.75 (6H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 192.3, 151.9, 149.0, 140.1, 138.0, 132.1, 132.0, 128.9, 126.2, 104.4, 101.0, 56.0, 55.5; MS (E) m/z 482 (M^+).

13. General procedure for the synthesis of acridines **10a**,**j**. The appropriate nitro compound (1 equiv., 0.02 mol) and tin powder (4 equiv.) were suspended in hydrochloric acid (10 mL, 36%). Ethanol (50 mL) was added and the solution was refluxed for 24 h. After cooling and neutralizing with base (KOH), the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. After extraction with water (3×100 mL), the solvent was stripped off and the crude product was purified chromatographically with the appropriate solvent. Compound **10a** was obtained according to the standard procedure. The crude product was purified chromatographically with a mixture of dichloromethane (98.5%) and methanol (1.5%), to afford **10a** in 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.25 (2H, s, 4,5-H acridine), 7.70–7.64 (m, 3H, 2,4,6-H phenyl), 7.48–7.44 (m, 2H, 3,5-H phenyl), 6.80 (s, 2H, 1,8-H acridine), 4.21 (6H, s, OCH_3), 3.78 (6H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 150.6, 136.8, 134.6, 130.2, 129.7, 129.6, 103.4, 99.4, 57.8, 56.0; MS (CI) m/z 376 (MH^+).