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Microwave-assisted synthesis of rufigallol and its novel room-temperature liquid crystalline derivatives

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Abstract—An efficient, simple, rapid and economic microwave-assisted synthesis of rufigallol, a molecule of both biological and physical interest, is reported. The acid-catalyzed self-condensation of gallic acid under microwave irradiation produces rufigallol in high yield within 90 s. Alkylation of rufigallol with branched-chain alkyl halides under microwave irradiation provides novel room-temperature discotic liquid crystals in excellent yield.

Rapid microwave-assisted chemical synthesis has attracted considerable attention in the past decade. This is not only due to the fact that many organic reactions proceed significantly faster and with greater selectivity than under thermal conditions but also because of the operational simplicity, high yield of products and cleaner reactions with easier work-up. A large number of review articles provide extensive coverage of the subject.[1]

Rufigallol is a molecule of both biological and materials science interest. Recently, it has been reported as a novel oxidant drug.[2,3] A remarkable synergistic antimalarial interaction between rufigallol and the structurally similar compound exifone has been described.[4] It is believed that rufigallol acts in pro-oxidant fashion to produce oxygen radicals inside parasitized erythrocytes.[4] Many polyhydroxyquinones including rufigallol have recently been identified as active antimalarial compounds.[2–4] Rufigallol has also been recognized for its vitamin K activity.[5]

On the other hand, rufigallol has been found to function as the core fragment for a remarkable family of discotic liquid crystals (DLCs). Rufigallol derivatives are one of the earliest systems reported to form columnar mesophases. They are interesting materials as these molecules have an elongated core with a twofold symmetry axis, they are coloured and exhibit important polymorphism, the core is electron deficient in nature, they are thermally stable and their chemistry is fairly straightforward. Billard and co-workers[6a] reported the first discotic liquid crystalline hexaesters of rufigallol in 1980 and since then about 100 different discotic liquid crystalline derivatives of this molecule have been prepared and studied.[6]

Robiquet reported the synthesis of rufigallol in very poor yield by the action of sulfuric acid on gallic acid as early as 1836[7] and Grimshaw and Haworth reported the purification of rufigallol in 1956.[8] Since then, little further work has appeared and no new efficient method to prepare rufigallol has been reported. We have observed that the self-condensation of gallic acid in the presence of sulfuric acid can be achieved in high yield in about one minute using microwave heating. The resultant rufigallol was converted to novel room-temperature discotic liquid crystalline derivatives by substitution with straight and/or branched-alkyl chains.

Rufigallol (**2**) was prepared by the self-condensation of gallic acid monohydrate (**1**) in sulfuric acid under microwave irradiation as shown in Scheme 1. The condensation was carried out using an unmodified domestic microwave oven (LG, MS-192W). However, commercial microwave reactors for organic reactions are now available which provide adequate mixing and control of reaction parameters such as temperature and pressure.[1] Irradiation (360 W) of gallic acid (2.0 g) in

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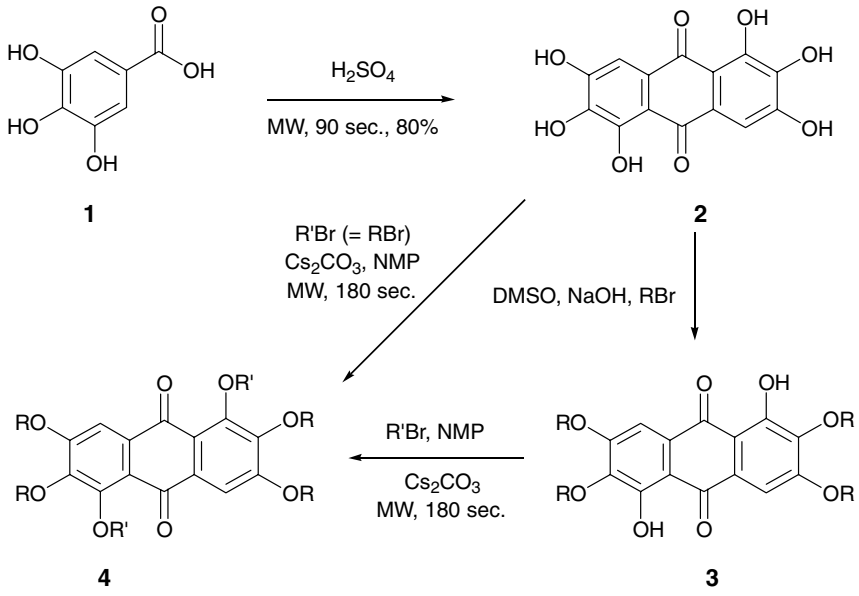

a: R = R' = -$CH_2CH_2CH(CH_3)(CH_2)_3CH(CH_3)_2$, 90%
b: R = C_6H_{13}; R' = -$CH_2CH_2CH(CH_3)(CH_2)_3CH(CH_3)_2$, 88%
c: R = C_7H_{15}; R' = -$CH_2CH_2CH(CH_3)(CH_2)_3CH(CH_3)_2$, 86%
d: R = C_8H_{17}; R' = -$CH_2CH_2CH(CH_3)(CH_2)_3CH(CH_3)_2$, 85%
e: R = C_9H_{19}; R' = -$CH_2CH_2CH(CH_3)(CH_2)_3CH(CH_3)_2$, 83%

Scheme 1. Synthesis of rufigallol (**2**) and its liquid crystalline derivatives.

6.0 mL of concentrated H_2SO_4 for 90 s yielded 1.4 g (84%) of rufigallol. The product was isolated simply by adding water to the reaction mixture followed by filtration of the solid product. This was converted to its hexaacetate[8] (60%) by treatment with acetic anhydride. Hydrolysis of the pure hexaacetate furnished pure rufigallol in an overall yield of about 50%.

Etherification of rufigallol **2** under mild conditions produced 1,5-dihydroxy-2,3,6,7-tetraalkoxy-9,10-anthraquinone **3** without alkylating the hydrogen bonded C-1 and C-5 positions.[6e] However, hexalkoxy-derivatives could be easily prepared by using an excess of alkyl halide and base. While a large number of DLCs have been derived from rufigallol, most of them display a mesophase at higher temperatures. For any device application, stability of the mesophase at ambient temperature is required and the mesophase should be stable over a wide temperature range. Efforts have been made to prepare a variety of room-temperature electron-rich DLCs, however, room-temperature electron-deficient DLCs are rare.[9] Therefore, it is of great practical interest to prepare rufigallol-based room-temperature electron-deficient DLCs.

The use of branched-alkyl chains to modify the thermal properties of various liquid crystalline materials has been well documented and some effects of the introduction of branched chains into mesogens on mesomorphism have been summarized by Ohta et al.[10] Collard and Lillya reported[11] that when the aliphatic side chains of hexa(*n*-alkanoyloxy)benzenes and hexakis(*n*-alkanoyloxy)cyclohexanes were branched, the columnar mesophase is widened but the type of mesophase formed was not affected. A similar strategy has been applied by Schouten et al. to phthalocyanine molecules.[12] The transition temperatures of hexabenzocoronene discotics were modified significantly by using branched peripheral chains.[13] We have previously utilized the branched-chain substitution strategy to stabilize the mesophase and lower the clearing temperature of tricycloquinazoline discotics,[9] and to prepare the first examples of discotic nematic liquid crystals.[14] The decrease in the transition temperature could be due to the disorder caused by branched chains and stereoheterogeneity.

In order to prepare novel room-temperature rufigallol discotics, we initially replaced all six peripheral *n*-alkyl chains with 3,7-dimethyloctyl chains. The reaction of rufigallol with 1-bromo-3,7-dimethyloctane in the presence of cesium carbonate under microwave heating produced **4a** within 3 min. However, it was found to be a non-liquid crystalline viscous oil. The replacement of only two *n*-alkyl chains at the 1- and 5-positions with branched alkyl chains under similar reaction conditions (Scheme 1) afforded products **4b–e** in good yields (83–88%). Thus, alkylation of 1,5-dihydroxy-2,3,6,7-tetraalkoxy-9,10-anthraquinone **3** with 1-bromo-3,7-dimethyloctane using cesium carbonate as base under microwave irradiation produced compounds **4b–e**[15] in about 180 s. Products **4b–e** were found to be liquid crystalline at room temperature. The phase transition temperatures of all the new compounds together with transition enthalpy values determined by DSC are given in Table 1. The transition temperatures and associated enthalpy values were determined using a differential

Table 1. Phase transition temperatures (peak, °C) and associated enthalpy changes (J/g, in parentheses) of novel rufigallol discotics

Compound	First heating scan	First cooling scan
4b	Col_h77.7 (10.6) I	I 76.1 (10.7) Col_h
4c	Col_h78.7 (9.9) I	I 76.4 (9.8) Col_h
4d	Col_h72.3 (8.9) I	I 70.4 (8.9) Col_h
4e	Col_h67.4 (7.3) I	I 65.4 (7.3) Col_h

Col_h: Hexagonal columnar phase; I: isotropic phase.

scanning calorimeter operated at a scanning rate of 5 °C min^{-1} both on heating and cooling. Textural observations of the mesophase were carried out using polarizing light microscopy.

Derivatives **4b–e** all displayed similar behaviour and, therefore, the thermal behaviour of only one representative member is described here. Compound **4b** on heating transforms to the isotropic phase at about 78 °C. On cooling this isotropic liquid, the well-defined texture of the Col_h phase appeared at about 77 °C and was stable at room temperature (Fig. 1). The DSC traces obtained on heating and cooling runs are shown in Figure 2. Compounds **4c–e** showed similar phase behaviour (Table 1).

The existence of the mesophase as a Col_h phase was confirmed from X-ray diffraction studies. The diffraction pattern was obtained at room temperature in the columnar phase for compound **4b**. The one-dimensional intensity versus 2θ profile is shown in Figure 3. In the small angle region, four sharp peaks were observed, taken in the ascending order of the diffraction angle, the *d*-spacing of the first reflection (lowest angle and highest intensity) to the other three is in the ratio of $1:1/\sqrt{3}:1/\sqrt{4}:1/\sqrt{7}$. These values correspond to that expected from a two-dimensional hexagonal lattice. In the wide angle region there were two diffused peaks; a broad one at $2\theta \sim 20°$ and another relatively narrow peak at higher

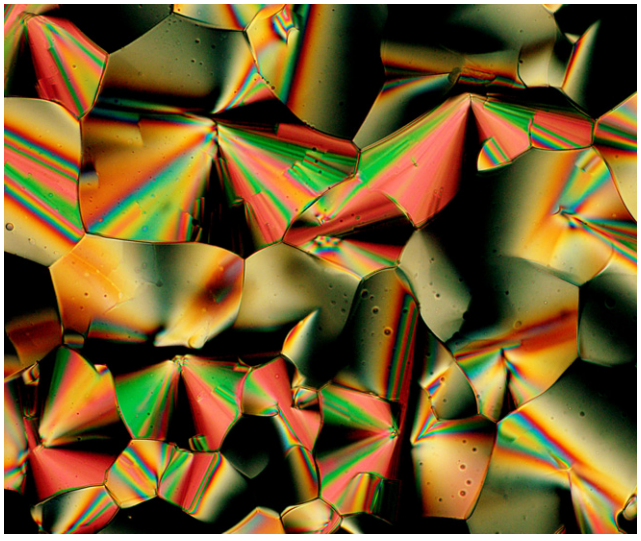

Figure 1. Optical photomicrograph of **4b** at 25 °C on cooling from the isotropic liquid (crossed polarizers, magnification × 200).

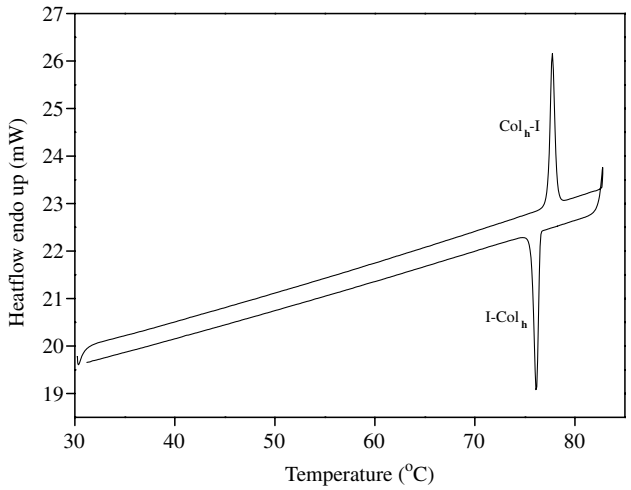

Figure 2. DSC traces for **4b** on heating and cooling (scan rate 5 °C min^{-1}).

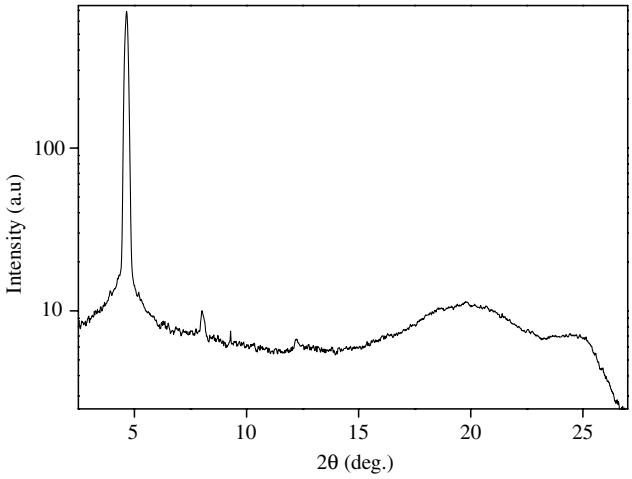

Figure 3. The one-dimensional intensity versus 2θ profile derived from X-ray diffraction for **4b** at 25 °C.

angles. The broad peak with a *d*-spacing of ~4.48 Å was due to the liquid-like packing of the aliphatic chains. The relatively narrow peak, which was separated from the broader one, corresponds to a spacing of 3.64 Å and was due to core-to-core (intracolumnar) separation. All the features fit into the well-known model for the Col_h phase, in which the disc-like molecules stack one on top of another to form columns and the columns in turn are arranged in a two-dimensional hexagonal lattice. Within a column, the chains have only liquid-like correlations while the molecular cores have a better positional order, albeit short-ranged, with an inter-core separation of 3.64 Å.

In conclusion, we have developed an efficient, simple, rapid and economic methodology for the synthesis of rufigallol. Suitable peripheral substitution leads to the synthesis of novel room-temperature electron-deficient discotic liquid crystals which are extremely important for many device applications such as light emitting diodes, photovoltaic solar cells, thin film transistors, etc.

References and notes

1. For recent reviews on microwave-assisted organic synthesis, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) Wiesbrock, F.; Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun.* **2004**, *25*, 1739–1764; (c) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128–141; (d) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578–1591; (e) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (f) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193–198; (g) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851–10870; (h) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234; (i) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432.
2. Ignatushchenko, M. V.; Winter, R. W.; Riscoe, M. *Am. J. Trop. Med. Hyg.* **2000**, *62*, 77–81.
3. Ziegler, J.; Linck, R.; Wright, D. W. *Curr. Med. Chem.* **2001**, *8*, 171–189.
4. Winter, R. W.; Cornell, K. A.; Johnson, L. L.; Ignatushchenko, M.; Hinrichs, D. J.; Riscoe, M. K. *Antimicrob. Agents Chemother.* **1996**, *40*, 1408–1411.
5. Martin, G. J.; Lischer, C. F. *J. Biol. Chem.* **1941**, *137*, 169–171.
6. For example see: (a) Queguiner, A.; Zann, A.; Dubois, J. C.; Billard, J. In *Proceedings of the International Conference on Liquid Crystals, Bangalore*; Chandrasekhar, S., Ed.; Heyden and Son: London, 1980; pp 34–40; (b) Carfugna, C.; Roviello, A.; Sirigu, A. *Mol. Cryst. Liq. Cryst.* **1985**, *122*, 151–160; (c) Werth, M.; Leisen, J.; Boeffel, C.; Dong, R. Y.; Spiess, H. W. *J. Phys. II France* **1993**, *3*, 53–67; (d) Billard, J.; Luz, Z.; Poupko, R.; Zimmermann, H. *Liq. Cryst.* **1994**, *16*, 333–342; (e) Raja, K. S.; Ramakrishnan, S.; Raghunathan, V. A. *Chem. Mater.* **1997**, *9*, 1630–1637; (f) Prasad, V.; Krishnan, K.; Balagurusamy, V. S. K. *Liq. Cryst.* **2000**, *27*, 1075–1085; (g) Kumar, S.; Naidu, J.; Varshney, S. K. *Mol. Cryst. Liq. Cryst.* **2004**, *411*, 355–362; (h) Gupta, M.; Dhar, R.; Agrawal, V. K.; Kumar, S. *Proc. SPIE (USA)*, in press.
7. Robiquet. *Annalen* **1836**, *19*, 204–210.
8. Grimshaw, J.; Haworth, R. D. *J. Chem. Soc.* **1956**, 4225–4232.
9. Kumar, S.; Rao, D. S. S.; Prasad, S. K. *J. Mater. Chem.* **1999**, *9*, 2751–2754.
10. Ohta, K.; Morizumi, Y.; Ema, H.; Fujimoto, T.; Yamamoto, I. *Mol. Cryst. Liq. Cryst.* **1991**, *208*, 55–63.
11. Collard, D. M.; Lillya, C. P. *J. Am. Chem. Soc.* **1991**, *113*, 8577–8583.
12. Schouten, P. G.; van der Pol, J. F.; Zwikker, J. W.; Drenth, W.; Picken, S. J. *Mol. Cryst. Liq. Cryst.* **1991**, *195*, 291–305; Schouten, P. G.; Warman, J. M.; deHaas, M. P.; van Nostrum, C. F.; Gelinck, G. H.; Nolte, R. J. M.; Copyn, M. J.; Zwikker, J. W.; Engel, M. K.; Hanack, M.; Chang, Y. H.; Ford, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 6880–6894.
13. Pisula, W.; Kastler, M.; Wasserfallen, D.; Mondeshki, M.; Paris, J.; Schnell, I.; Mullen, K. *Chem. Mater.* **2006**, *18*, 3634–3640.
14. Kumar, S.; Varshney, S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3140–3142; Kumar, S.; Varshney, S. K.; Chauhan, D. *Mol. Cryst. Liq. Cryst.* **2003**, *396*, 241–250.
15. *Synthesis of* **2**: Gallic acid (2.0 g) and sulfuric acid (6 mL) were taken in a glass vial, which was loosely sealed with a rubber septum and then irradiated in a microwave oven (360 W) for 15 s. The vial was removed from the oven and left to stand for about 1 min. This process was repeated six times and then the reaction mixture was poured into ice-water. The resultant solid was collected by filtration and washed repeatedly with water until neutral and then dried to afford **2** in 80% yield (1.37 g). *Synthesis of* **4a**: rufigallol (1.0 mmol), caesium carbonate (12 mmol), 3,7-dimethyl-1-bromooctane (12 mmol) and NMP (0.5 mL) were mixed in a glass vial. The vial was loosely sealed with a rubber septum and then irradiated in a microwave oven for 30 s. The vial was removed from the oven and left to stand for about 1 min, this process was repeated six times. The reaction mixture was poured into cold water and the product extracted with dichloromethane. The organic extract was dried, concentrated and the product purified by column chromatography over silica gel to afford 90% of **4a**. *Synthesis of* **4b–e**: The tetraalkoxy-rufigallols **3** were prepared using reported conditions.[6e] In a vial containing tetrahexyloxy-rufigallol (0.1 g, 0.156 mmol), caesium carbonate (0.2 g, 0.62 mmol) and 3,7-dimethyl-1-bromo octane (0.14 g, 0.62 mmol) was added NMP (0.5 mL). Alkylation was carried out as described above for the synthesis of **4a**. Yields of the pure products are given in Scheme 1. Selected data for compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 2H, Ar–H), 4.11 (m, 12H, Ar–OCH_2–), 1.1–2.1 (m, 52H, aliphatic CH_2), 0.96 (d, 6H, $J = 6.2$ Hz, CH_3), 0.92 (t, 12H, $J = 6.7$ Hz, CH_3), 0.86 (d, 12H, $J = 6.6$ Hz, CH_3), derivatives **4c–e** showed similar spectra except for different numbers of aliphatic protons; ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.2, 157.5, 154.0, 147.0, 132.7, 120.4, 107.0, 74.1, 73.3, 69.2, 39.4, 37.5, 31.7, 31.5, 30.3, 29.9, 29.0, 28.0, 25.7, 24.7, 22.6, 19.7, 14.0; derivatives **4c–e** showed similar spectra; IR (KBr, derivatives **4b–4e** showed similar spectra): ν_{max} 2924, 2852, 1666, 1572, 1464, 1377, 1319, 1265, 1130, 1096, 1040, 978, 876, 721 cm^{-1}; UV ($CHCl_3$, derivatives **4b–e** showed similar spectra): λ_{max} 285.6, 317.2, 354.4 nm. Elemental analysis: **4b**: Calcd for $C_{58}H_{96}O_8$: C, 75.61; H, 10.50. Found: C, 75.87; H, 10.26; **4c**: Calcd for $C_{62}H_{104}O_8$: C, 76.18; H, 10.72. Found: C, 75.92; H, 11.0; **4d**: Calcd for $C_{66}H_{112}O_8$: C, 76.69; H, 10.92. Found: C, 76.47; H, 11.25; **4e**: Calcd for $C_{70}H_{120}O_8$: C, 77.15; H, 11.10. Found: C, 77.29; H, 11.09.