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Synthesis of a halo-methylphenylene periphery-functionalized triazine-based dendritic molecule with a 3,3′-dimethyl-biphenyl linker using tris(halo-methylphenylene)triazines as building blocks

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ABSTRACT

A tris(bromo-methylphenylene)triazine and its corresponding phosphine oxide derivative have been synthesized; the latter compound was found to be a potent ligand for the hydroformylation reaction. Suzuki coupling of the mono-pinacolboronate derivative of the former compound with a tris(iodo-methylphenylene)triazine was possible at two of the three iodine atoms, yielding a bromo- and iodo-methylphenylene periphery-functionalized triazine-based dendritic molecule with a 3,3′-dimethyl-biphenyl linker.

Dendrimers and dendritic molecules are the subject of significant academic and industrial interest.[1,2] Compounds containing *s*-triazine units and dendrimers based on triazine have received a remarkable amount of attention owing to their potential applications[3] and have shown molecular recognition and self-assembly properties.[4] They are of interest for their electroluminescent and electrochemical properties due to the role of the electron-deficient triazine unit as an electron transport component[5] and also for their liquid-crystalline and nonlinear optical properties.[5b,6] Triazine dendritic structures, and in particular those based on melamine, have shown very promising results for drug delivery and can sequester a range of hydrophobic guests effectively, including candidate anticancer drugs, and with the absence of toxicity.[7]

Triazine dendrimers can be synthesized by various routes based on divergent and convergent methods. The most common methods are cycloaddition reactions to form the triazine ring, cyclotrimerization of organic cyanates and nucleophilic aromatic substitution of cyanuric chloride.[1–8] In the great majority of triazine dendritic molecules, the triazine rings are linked by nitrogen-containing spacers such as amino groups. In this Letter, we report the synthesis of a halo-methylphenylene periphery-functionalized triazine-based dendritic molecule with a 3,3′-dimethyl-biphenyl linker, by the use of tris(halo-methylphenylene)triazines as building blocks. We used compound **2** with a methyl substituent instead of the analogue without the methyl group due to its higher solubility in organic solvents. Indeed, we found that in boiling toluene, the solubility of **2** was 2.8 g/100 mL compared to 0.8 g/100 mL for the analogue without methyl substituents.

The synthesis of the title dendritic molecule was first attempted by cyclotrimerization of the corresponding nitrile as shown in Scheme 1. The tris(bromoaryl)triazine **2** was prepared in high yield by cyclotrimerization of 4-bromo-3-methylbenzonitrile **(1)** with neat trifluoromethanesulfonic acid. The procedure was analogous to that previously described for the cyclotrimerization of 4-bromobenzonitrile.[9] The CH_3 resonance in **2** was observed as one signal in the ^1H and ^{13}C NMR spectra at δ 2.57 and 23.17, respectively, indicating the equivalence of the three CH_3 groups. Compound **2** could be regarded as the 0th generation of a symmetric halo-methylphenylene periphery-functionalized triazine dendrimer. In the next step, cyanation of **2** was achieved by the use of $Pd_2(dba)_3$, dppf and Zn as the catalyst and $Zn(CN)_2$ as the cyanide source, in accordance with a known protocol for the cyanation of aryl chlorides.[10] Although the ratio of Br/CN was kept at 2.5:1, cyanation was not selective, leading to unreacted **2** (32%) and a mixture of mono- and dicyanated derivatives **3** and **4**, in yields of 30% and

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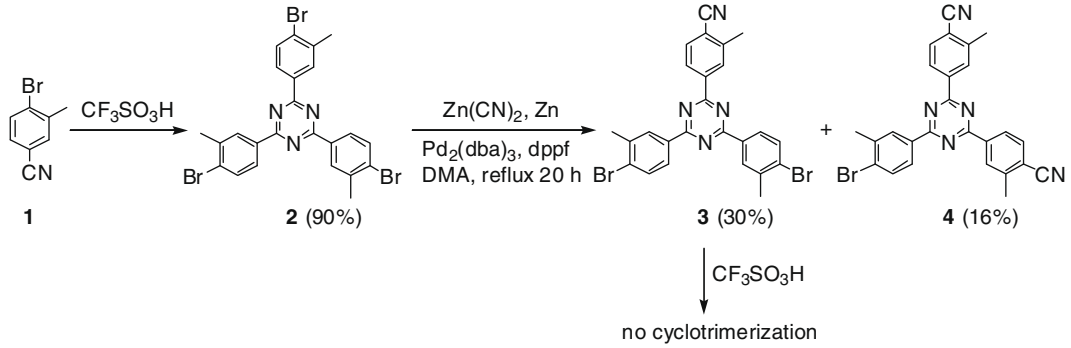
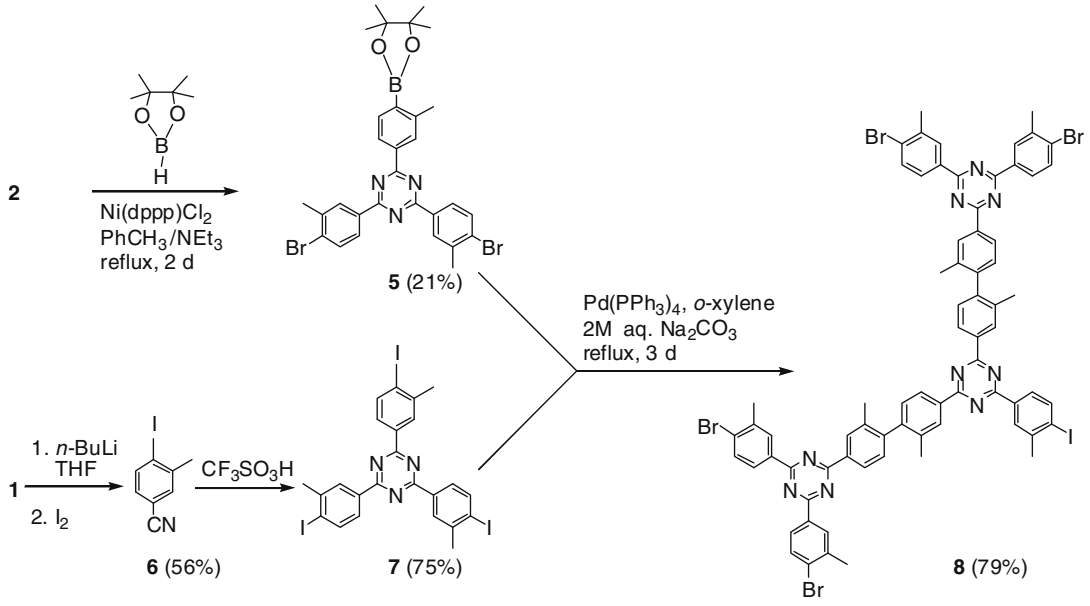


Scheme 1.

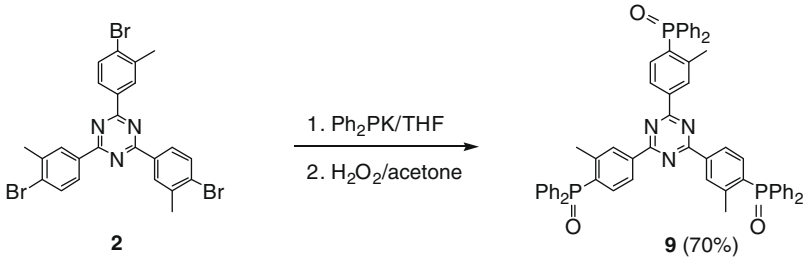
16%, respectively. Unfortunately, the formation of the 1st generation dendrimer by cyclotrimerization of **3**, as described for **1**, was not possible, probably due to steric hindrance.

The formation of the 1st generation dendrimer was then attempted via a Suzuki coupling of an aryl halide and a pinacolboronate in a mixture of an organic solvent and an aqueous solution of Na_2CO_3 using $Pd(PPh_3)_4$ as the catalyst (Scheme 2), in accordance with the synthesis of hyperbranched polyphenylene by the homocoupling of (3,5-dibromophenyl)boronic acid.[11] The pinacolboronate **5** was synthesized by the nickel-catalyzed reaction of **2** with pinacolborane using $Ni(dppp)Cl_2$ in refluxing $PhCH_3/NEt_3$, as previously described for the synthesis of pinacolboronates by reaction of di- or tribromobenzene with pinacolborane.[12] A ratio of Br/B of 2.3:1 afforded **5** in 21% yield after two days refluxing. Palladium-catalysis using $Pd_2(dba)_3$/2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl was also attempted, however, without any improvement in the yield. In order to avoid homocoupling of **5** to give a mixture of hyperbranched polymers, the Suzuki coupling was performed between **5** and tris(iodoaryl)triazine **7** instead of the bromo-analogue **2**, since it is known that the reaction of arylboronic acid (or ester) proceeds at a higher rate with iodoarenes than with bromoarenes.[13] The tris(iodoaryl)triazine **7** was synthesized as described for **2**, by cyclotrimerization of 4-iodo-3-methylbenzonitrile **(6)**, prepared via bromine–lithium exchange in **1**, and further treatment with iodine. Suzuki coupling of the boronate **5** with the iodide **7** using $Pd(PPh_3)_4$ as the catalyst afforded the dendritic molecule **8** in 79% yield. Although the ratio of B/I was 1.3:1, coupling to only two of the three iodine atoms was achieved, presumably due to steric hindrance. This result is in contrast to the full coupling of arylboronic acid dendrimer arms to tribromobenzene[14] or the coupling of 4-(2,2′-dipyridylamino)phenylboronic acid to tris(4-bromophenyl)-1,3,5-triazine.[5d] The structure of **8** was determined by spectroscopic techniques. In the ^1H NMR spectrum, the ratio of the total number of aromatic protons to the total number of CH_3 protons was 1:1, and the ratio of the $5 \times CH_3$ protons closest to the halogens (δ 2.57) to the CH_3 protons attached to the other four aromatic rings (δ 2.30) was found to be 15:12, as expected for **8**. In the ^{13}C NMR spectrum, the CH_3 resonances were present as three signals at δ 29.70, 23.14 and 20.06, which were assigned to the CH_3 groups closest to iodine, bromine and the internal CH_3 groups, respectively.

The halogen atoms in compounds **2** and **8** can serve for further functionalization such as phosphorous-functionalized dendritic molecules, and thus, these reagents may be regarded as potent ligands for transition-metal homogeneous catalysis.[15] For example, we synthesized the phosphine oxide derivative **9** as shown in Scheme 3.[16] Replacement of the bromine atoms by the diphenylphosphine oxide group was achieved by reaction of **2** with potassium diphenylphosphide and subsequent oxidation of the resulting tris(triarylphosphine)triazine by hydrogen peroxide. The presence of only one singlet at δ 31.84 in the ^{31}P NMR spectrum of **9** clearly indicated the equivalence of the three phosphorous



Scheme 2.



Scheme 3.

atoms. Initial investigation of **9** as a ligand in the rhodium-catalyzed hydroformylation of styrene provided encouraging preliminary results, as the chemoselectivity of the reaction for aldehydes was quantitative and the regioselectivity towards the branched aldehyde was up to 98%.

In summary, Suzuki coupling of a pinacolboronate bis(bromomethylphenylene)triazine to two of the three iodine atoms was possible with tris(iodo-methylphenylene)triazine **7**, yielding a new dendritic molecule in which the triazine rings are linked by a 3,3′-dimethyl-biphenyl spacer. The presence of the halogen atoms on the periphery can serve for further functionalization, providing new reagents which may be useful in a wide range of dendrimer applications.

2,4,6-Tris(4-bromo-3-methyl-phenylene)-1,3,5-triazine (**2**): 4-Bromo-3-methylbenzonitrile **(1)** (11.0 g, 56.0 mmol) was added in small portions over 4 h to stirred trifluoromethanesulfonic acid (18.0 mL, 203.4 mmol) under argon at 0–5 °C, and then stirring was continued at this temperature for an additional 1 h and at room temperature for 1 h. The resulting orange solution was allowed to stand at room temperature overnight and then poured onto ice, yielding a white solid. The mixture turned alkaline on addition of 25% aqueous ammonium hydroxide, and the solid precipitate was removed by filtration, washed several times with water and dried under vacuum at 100 °C. The final traces of water were removed by azeotropic distillation with toluene, and the product was recrystallized from boiling toluene and dried under vacuum at 100 °C, yielding **2** as a white solid (9.9 g, 90%).[17] ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.54 (d, ^4J = 1.8 Hz, 3H, Ar*H*), 8.38 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 3H, Ar*H*), 7.72 (d, ^3J = 8.5 Hz, 3H, Ar*H*), 2.57 (s, 9H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 171.11 (triazine C), 138.40, 135.04, 132.77, 130.86, 130.18 and 127.76 (Ar), 23.17 (CH_3). Anal. Calcd for $C_{24}H_{18}Br_3N_3$: C, 49.01; H, 3.08; N, 7.14. Found: C, 48.74; H, 2.96; N, 6.92.

2,4-Bis(4-bromo-3-methyl-phenylene)-6-(4-cyano-3-methyl-phenylene)-1,3,5-triazine (**3**) *and 2-(4-bromo-3-methyl-phenylene)-4,6-bis(4-cyano-3-methyl-phenylene)-1,3,5-triazine* (**4**): A mixture of **2** (2.94 g, 5.00 mmol), Zn dust (0.04 g, 0.60 mmol), $Zn(CN)_2$ (0.35 g, 3.00 mmol), $Pd_2(dba)_3$ (0.09 g, 0.10 mmol), dppf (0.11 g, 0.20 mmol) and DMA (100 mL) was heated at reflux under argon for 20 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (500 mL), washed with 2 N aq NH_4OH solution (100 mL) and brine (100 mL) and dried over Na_2SO_4. After filtration, the filtrate was passed through a pad of Celite and the solvents were removed by evaporation. Column chromatography over silica gel using mixtures of dichloromethane/hexane (initially 1:1, then 3:1, then 5:1) and finally dichloromethane yielded the starting material **2** (0.94 g, 32%) and the cyanated products **3** (0.81 g, 30%)[17] and **4** (0.39 g, 16%).[17] Compound **3**: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.62–8.54 (m, 4H, Ar*H*), 8.38 (d, ^3J = 8.6 Hz, 2H, Ar*H*), 7.79 (d, ^3J = 7.9 Hz, 1H, Ar*H*), 7.73 (d, ^3J = 8.6 Hz, 2H, Ar*H*), 2.72 (s, 3H, CH_3), 2.57 (s, 6H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 171.43 (triazine C), 142.41, 139.79, 138.56, 134.71, 132.90, 132.80, 130.90, 130.54, 130.18, 127.79, 126.56 and 125.62 (Ar), 116.21 (CN), 23.17 and 20.74 (CH_3). Anal. Calcd for $C_{25}H_{18}Br_2N_4$: C, 56.20; H, 3.40; N, 10.49. Found: C, 55.99; H, 3.39; N, 10.30. Compound **4**: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.65–8.57 (m, 5H, Ar*H*), 8.41 (d, ^3J = 7.9 Hz, 1H, Ar*H*), 7.82 (d, ^3J = 7.9 Hz, 2H, Ar*H*), 7.75 (d, ^3J = 8.6 Hz, 1H, Ar*H*), 2.74 (s, 6H, CH_3), 2.59 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 170.65 (triazine C), 142.51, 139.47, 138.72, 134.39, 132.99, 132.87, 130.90, 130.25, 129.86, 127.85, 126.62 and 124.07 (Ar), 116.53 (CN), 23.17 and 20.74 (CH_3).

2-[4-(4,4′,5,5′-Tetramethyl-1,3,2-dioxaborolyl)]-4,6-di(4-bromo-3-methyl-phenylene)-1,3,5-triazine (**5**): A solution of **2** (7.42 g, 12.62 mmol), 4,4′,5,5′-tetramethyl-1,3,2-dioxaborolane (pinacolborane) (2.40 mL, 16.54 mmol), Ni(dppp)Cl_2 (0.21 g, 0.39 mmol) in toluene (300 mL) and triethylamine (7 mL) was refluxed under argon for 2 d, during which time a precipitate was formed, presumably NEt_3·HBr. After cooling to room temperature, the mixture was quenched with saturated aqueous NH_4Cl solution (120 mL), the organic layer was separated, diluted with dichloromethane (200 mL) and washed with saturated aqueous NH_4Cl solution (120 mL). The combined aqueous layers were extracted with dichloromethane (200 mL). The combined organic layers were washed with water (120 mL) and dried over Na_2SO_4. After filtration, the filtrate was passed through a pad of Celite and the solvents were removed by evaporation. Column chromatography over silica gel using dichloromethane/hexane (1:1) and then dichloromethane as eluent yielded the starting material **2** (3.02 g, 41%) and **5** as a white solid (1.68 g, 21%).[17] ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.42–8.37 (m, 4H, Ar*H*), 8.26 (d, ^3J = 8.6 Hz, 2H, Ar*H*), 7.91 (d, ^3J = 7.3 Hz, 1H, Ar*H*), 7.63 (d, ^3J = 8.6 Hz, 2H, Ar*H*), 2.68 (s, 3H, Ar–CH_3), 2.51 (s, 6H, Ar–CH_3), 1.40 (s, 12H, C(CH_3)$_2$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 171.53 and 170.72 (triazine C), 145.00, 138.11, 137.59, 135.97, 135.07, 132.54, 130.73, 129.89, 129.63, 127.63 and 125.01 (Ar), 83.70 (*C*(CH_3)$_2$), 24.92 (C(*C*H_3)$_2$), 23.11 (Ar–*C*H_3), 22.39 (Ar–*C*H_3). Anal. Calcd for $C_{30}H_{30}BBr_2N_3O_2$: C, 56.73; H, 4.76; N, 6.62. Found: C, 57.01; H, 4.95; N, 6.34.

4-Iodo-3-methylbenzonitrile (**6**): To a solution of **1** (5.00 g, 25.50 mmol) in THF (150 mL) under argon was added *n*-BuLi (1.78 M in methylcyclohexane, 15.50 mL, 27.59 mmol) at −65 °C, and the solution was stirred at this temperature for 2 h. Next, excess solid iodine (13.58 g, 53.50 mmol) and additional THF (40 mL) were added, and the reaction mixture was warmed slowly to room temperature and stirred overnight, after which an aqueous solution of sodium thiosulfate (40.00 g, 161.17 mmol in 100 mL of water) was added. The volatile materials were removed by evaporation, the residue was extracted with dichloromethane (2 × 200 mL), the combined organic layers were washed with water (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness to yield a yellow–brown solid, which was recrystallized from ethanol yielding **6** as a white solid (3.46 g, 56%), mp 73–75 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.92 (d, ^3J = 8.5 Hz, 1H, Ar*H*), 7.47 (s, 1H, Ar*H*), 7.13 (d, ^3J = 7.9 Hz, 1H, Ar*H*), 2.46 (s, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 143.09, 139.86, 132.25 and 130.18 (Ar), 118.28 (CN), 112.13 (Ar–*C*–CN), 107.25 (Ar–*C*–I), 28.05 (CH_3).

GC–MS (EI): *m/z* (relative intensity) 243 (M^+, 100), 116 ($[M–I]^+$, 21), 89 (17), 63 (8). Anal. Calcd for C_8H_6IN: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.78; H, 2.57; N, 5.53.

2,4,6-Tris(4-iodo-3-methyl-phenylene)-1,3,5-triazine (**7**): Reaction of **6** (2.16 g, 8.89 mmol) with trifluoromethanesulfonic acid (2.80 mL, 31.64 mmol) as described for the synthesis of **2** yielded **7** as a white solid (1.61 g, 75%).[17] ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ 8.60 (s, 3H, Ar*H*), 8.26–8.23 (m, 3H, Ar*H*), 8.06 (d, ^3J = 8.0 Hz, 3H, Ar*H*), 2.62 (s, 9H, CH_3). Anal. Calcd for $C_{24}H_{18}I_3$: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.40; H, 2.24; N, 5.84.

Dendritic molecule **8**: A solution of **7** (0.25 g, 0.34 mmol), **5** (0.85 g, 1.34 mmol) and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) in *o*-xylene (25 mL) and aqueous Na_2CO_3 (2 M, 2.60 mL, 5.20 mmol) was refluxed under argon for 3 d. After cooling to room temperature, the mixture was quenched with saturated aqueous NH_4Cl solution (50 mL) and diluted with dichloromethane (300 mL). The organic layer was separated, washed with water (50 mL) and dried over Na_2SO_4. After filtration, the filtrate was passed through a pad of Celite and the solvents were removed by evaporation. Column chromatography over silica gel using dichloromethane/hexane (1:1) as eluent yielded **8** as a white solid (0.40 g, 79%).[17] ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.74–8.59 (m, 17H, Ar*H*), 7.71 (m, 5H, Ar*H*), 7.39 (m, 5H, Ar*H*), 2.57 (s, 15H, CH_3), 2.30 (s, 12H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 171.69 and 171.11 (triazine C), 145.52, 138.37, 136.27, 135.65, 135.26, 132.77, 130.93, 130.47, 130.12, 129.53, 127.79 and 126.56 (Ar), 29.70, 23.14 and 20.06 (CH_3).

2,4,6-Tris(4-diphenylphosphinyl-3-methyl-phenylene)-1,3,5-triazine (**9**): A solution of potassium diphenylphosphide in THF (0.5 M, 7 mL, 3.50 mmol) was added to a white suspension of **2** (0.59 g, 1.00 mmol) in THF (15 mL) at room temperature under argon, and then heated at reflux for 48 h. The reaction mixture was cooled to room temperature, diluted by the addition of dichloromethane (60 mL), washed with 10% aqueous NaOH (2 × 20 mL), then with brine and dried over Na_2SO_4. The volatiles were evaporated and the residue was evacuated at 180 °C. The remaining very viscous oil turned to a solid on addition of ether/hexane (1:1, 10 mL), and the solid was removed by filtration, washed with ether/hexane and dried under vacuum at 180 °C. The solid was mixed with acetone (50 mL) and 30% hydrogen peroxide (9 mL, 88.15 mmol) and refluxed for 1 h in air. After cooling to room temperature, the volatiles were evaporated under reduced pressure, the residue was dissolved in a minimum amount of dichloromethane, and slow diffusion of ether afforded a solid which was then washed twice with ether/dichloromethane (10:1) and then with ether yielding **9** (0.67 g, 70% based on **2**).[17] ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.57–8.46 (m, 6H, Ar*H*), 7.67–7.19 (m, 33H, Ar*H*), 2.58 (s, 9H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 171.27 (triazine C), 144.00–125.56 (Ar), 21.88 (CH_3). ^{31}P NMR (121.50 MHz, $CDCl_3$): δ 31.84 (s). Anal. Calcd for $C_{60}H_{48}N_3O_3P_3$: C, 75.70; H, 5.08; N, 4.41. Found: C, 75.92; H, 5.03; N, 4.67.

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17. The mp apparatus used has an upper limit of 200 °C. Compounds **2**–**5** and **7**–**9** did not melt below 200 °C.