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A colored dendrimer as a new soluble support in organic synthesis. Part 1: Suzuki reaction

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Abstract—A new strategy using a colored dendrimer as visible soluble support for organic synthesis has been developed. The efficiency of this new system has been demonstrated by the use of DR^{9}_{HMPA}–CH_2OH as the support in a Suzuki coupling reaction. Due to the visibility of the support, following of the reaction has been rendered easier and the purification time of the crude product has been considerably shortened. © 2001 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry has become an important component of the drug discovery process. Solid-phase syntheses based on modified polystyrene microbeads, originally introduced by Merrifield, have revolutionized organic synthesis in the construction of small molecule combinatorial libraries. The most important feature of solid-phase synthesis is the ease with which reagents and solvents are removed by a simple washing, which allows an easy automation of the synthetic procedure and therefore is transforming, together with other new synthesis technologies like parallel synthesis, traditional medicinal chemistry into high throughput medicinal chemistry. Despite its big success, solid support synthesis exhibits a certain number of problems due to the heterogeneous nature of the reactions and the low loading capacity of functional groups. Although more and more organic reactions can be carried out with solid supports, the task of modifying solution phase chemistry to the solid phase remains arduous and time consuming. The quantity of final product is often small, which often does not satisfy the requirement of in vitro and in vivo biological assays. The process is further handicapped by the difficulty in routinely monitoring solid phase reactions even though analytical technologies are improving. To address these issues, some alternatives using soluble polymeric supports have been developed by different groups, which could take advantage of both solution and solid-phase chemistry. (i) Soluble support chemistry, which did not require adaptation of the chemistry to solid phase. (ii) Reactions that could be followed by conventional TLC. (iii) Intermediates which could be routinely characterized by classical analytical methods, including ^{1}H and ^{13}C NMR, IR and mass spectrometry. (iv) Large reagent excess that could be used to drive reactions to completion. (v) Purifications that could be realized according to differences of physicochemical properties of small organic reagents and soluble polymeric supports, e.g. by precipitation/crystallization, ultra-filtration and especially size exclusion chromatography (SEC), which could be automated.[1]

The first class of soluble supports is the linear monomethylated polyethylene glycol (typically MPEG5000), soluble in many organic solvents and easily precipitated in non-polar solvents (e.g. Et_2O).[2] However, due to their linear topology, they provide only poor loading capacity. The second class of soluble supports is that of the low generation dendrimers and hyper-branched macromolecules. Dendrimers are highly branched, globular, monodispersed macromolecules. They comprise a core, branching units and a large number of terminal groups. They provide a very high loading capacity since they can bring multiple copies of molecules per dendrimer. They can be purified either by precipitation or by SEC. The commercially available polyamidoamine (PAMAM) has been successfully used by Kim and co-workers as a highly soluble support in the synthesis of indoles.[3] The use of other dendrimers or hyper-branched macromolecules has also been reported by other research groups.[4] Recently, we published an efficient divergent synthesis of generation-1 (G1) dendrimers **1** (Scheme 1), which include dye Red-1 in the core and nine *t*Boc-protected primary

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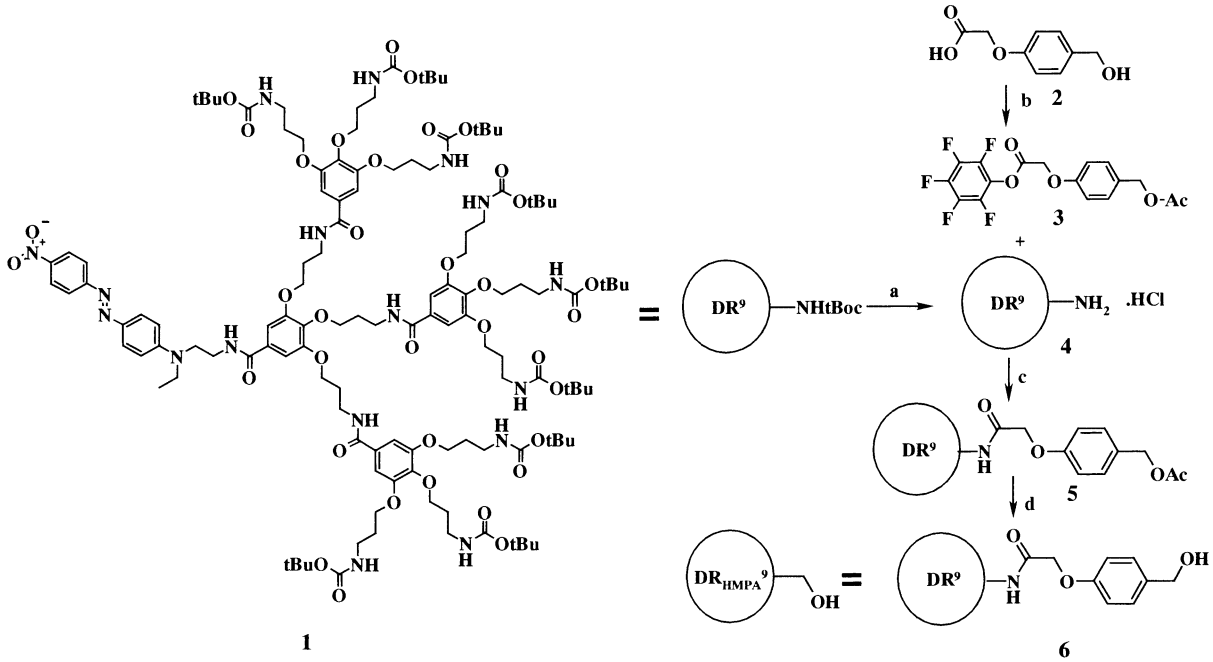


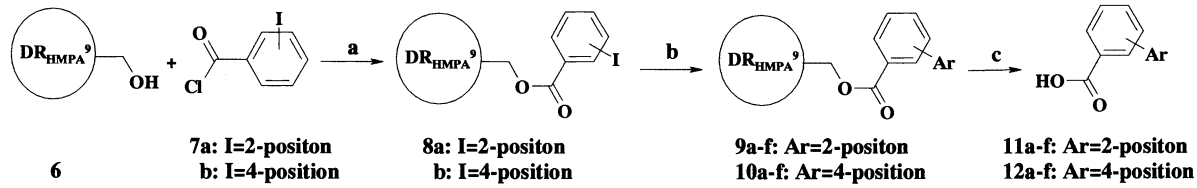
Scheme 1. *Reagents and conditions*: (a) HCl (g), AcOEt, 100%; (b) (i) Ac_2O, Py, (ii) C_6F_5OH, DCC, DMF, 50%; (c) TEA, DMF, 91%; (d) K_2CO_3, MeOH–CH_2Cl_2, 72%.

amines.[5] The fact that the dye Red-1 was incorporated into the dendrimer confers to them an advantage over most dendrimers, which is their color. This new additional property together with the chemically functionalizable terminal *t*Boc-protected primary amines make them interesting targets in our research to find new carriers, for example, for active entities and/or antibodies. Herein we would like to report our studies on the use of this visible soluble support in organic synthesis, which simplifies the follow-up of the reaction and shortens purification times.

For this purpose, the Suzuki reaction has been chosen as an example. The red dendrimer **1** (DR^9–NH*t*Boc: D = dendrimer, R = Red and nine terminal groups) was treated with gaseous HCl in EtOAc at 0°C for 1 h to give dendrimer **4**. The commercially available hydroxymethylphenoxyacetic acid **2** was acetylated by treatment with Ac_2O in pyridine, and treated with pentafluorophenol in the presence of DCC in DMF to afford the activated ester **3**. Coupling of **4** and **3** in the presence of TEA in DMF yielded dendrimer **5**, which was then deprotected with K_2CO_3 in a mixture of MeOH/CH_2Cl_2 (60/40). The desired dendrimer **6** with the HMPA-linker (DR^9_{HMPA}–CH_2OH) was obtained as a red solid (Scheme 1).

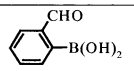
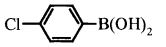
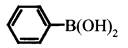
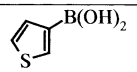
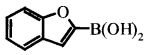
The attachment of 2-iodobenzoyl and 4-iodobenzoyl to DR^9_{HMPA}–CH_2OH **6** was realized in pyridine with, respectively, 2-iodobenzoyl chloride **7a** and 4-iodobenzoyl chloride **7b** to afford after purification on a Sephadex LH-20 SEC cartridge dendrimers **8a**,**b** (Scheme 2). The Suzuki reaction with six commercial available boronic acids was performed in DMF in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 (2 M in H_2O). The reaction mixture was extracted with AcOEt and washed with water to eliminate inorganic salts. The organic phase was concentrated under vacuum, and purified on a Sephadex LH-20 SEC cartridge to give the corresponding dendrimers **9a–f** and **10a–f** (Table 1). It was worth noticing that purification aided by the color indication took less than 30 min and all the products were characterized with conventional analytical methods (e.g. TLC).

To cleave the final compound from the dendrimer support, the commonly used TFA/CH_2Cl_2 method was adopted. The dendrimers **9a–f** and **10a–f** were treated by TFA in CH_2Cl_2 at rt for 1 h, when the deprotection was complete, as indicated by TLC, the reaction mixture was evaporated under vacuum, the residue was solubilized in a mixture of CH_2Cl_2/MeOH (60/40), treated with K_2CO_3 overnight, and taken into a mixture



Scheme 2. *Reagents and conditions*: (a) **7a**,**b**, Py, rt, 97% (**8a**) and 90% (**8b**); (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3 (2 M), DMF, 120°C, 59–100%; (c) TFA, CH_2Cl_2, 33–73%.

Table 1. Yields (%) of Suzuki coupling and cleavage

	Boronic Acid	Iodide	9a-f	11a-f	Iodide	10a-f	12a-f
a		ORTHO (**8a**)	82	50	PARA (**8b**)	95	59
b			90	66		86	57
c			89	73		86	50
d			100	46		94	70
e			59	45		85	61
f			89	33		94	58

of CH_2Cl_2/NaOH (1N). The insoluble red dendrimer was filtered, the aqueous solution was washed twice with CH_2Cl_2, acidified with HCl (1N), and extracted with AcOEt. The desired acids **11a–f** and **12a–f** were obtained as white solids. All products gave satisfactory analytical spectra (Table 1).[6]

In conclusion, the colored dendrimer DR^9_{HMPA}–CH_2OH proved to be a good choice for supporting an acid derivative, as demonstrated with the Suzuki reaction. The reaction could be easily carried out in an organic solvent in a homogenous way and it could be followed by TLC. The purification could be efficiently performed on Sephadex LH-20 SEC cartridges, and due to the coloration, it is easy to collect the red fraction. This shortened the purification time by SEC (less than 30 min), and the time of TLC analysis. We are currently studying the introduction of other linkers to the dendrimer DR^9–NH*t*Boc, application to other reactions and the way to automate the system for parallel synthesis and parallel purification.

Acknowledgements

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6. (a) Preparation of DR^9_{HMPA}–CH_2OH **6**: Step 1: To a red suspension of dendrimer **1** (2.57 g, 1.02 mmol) in 10 ml of AcOEt, was added at 0°C under nitrogen, 20 ml of HCl (g, 6 M) in AcOEt. The reaction mixture was allowed to reach rt slowly, and then evaporated to dryness under vacuum to give 1.97 g of the desired dendrimer **4** (yield: 100%). Step 2: To 60 ml of DMF, under nitrogen and at rt, was added 2.0 g of dendrimer **4** (1.03 mmol), 2.44 ml of TEA (17.5 mmol) and 4.84 g of activated ester **3** (12.4 mmol). The mixture was allowed to stand at rt for 48 h and diluted in AcOEt (200 ml), the organic layer was washed with NaOH (1N), H_2O (saturated NaCl), and evaporated to dryness under vacuum to yield 3.26 g of dendrimer **5** (91%). Step 4: To a mixture of MeOH–CH_2Cl_2 (250 ml, 6:4), was added dendrimer **4** (3.26 g, 0.94 mmol) and anhydrous K_2CO_3 (2.34 g, 16 mmol), at rt and under a nitrogen. The reaction mixture was stirred for 5 h and evaporated to eliminate the solvents. The residue was taken into of mixture of H_2O–CH_2Cl_2 (100 ml:50 ml), the precipitate formed at the interface was filtered, washed with H_2O, CH_2Cl_2 and Et_2O to afford, after drying, compound **6** (2.09 g, 72%). Data for **6**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (t, $J=7$ Hz, 3H), 1.81–1.90 (m, 18H), 1.93–12.02 (m, 6H), 3.30–3.35 (m, 18H), 3.47–3.49 (m, 8H), 3.51 (m, 2H), 3.59 (m, 2H), 3.99–407 (m, 24H), 4.38 (br d, $J=5.5$ Hz, 18H), 4.41 (br s, 18H), 5.04 (br t, $J=5.5$ Hz, 9H), 6.87 (app.d, $J=8.5$ Hz, 18H), 6.96 (app.d, $J=9$ Hz, 2H), 7.17 (br s, 8H), 7.19 (app.d, $J=8.5$ Hz, 18H), 7.83 (app.d, $J=9$ Hz, 2H); 7.92 (app.d, $J=9$ Hz, 2H), 8.08 (br t; $J=5.5$ Hz, 3H), 8.17 (br t; $J=5.5$ Hz, 6H), 8.18 (br s; 1H), 8.34 (app.d, $J=9$ Hz, 2H), 8.52 (br s, 2H), 8.64 (br s; 4H); MS (LSIMS): $[M+H]^+=3083.9^+$; IR (Nujol) 3150–3500, 1653, 1600, 1583, 1541, 1506 cm^{-1}; (b) General procedure for attachment of acyl chloride to **6**, ex. **8a**: To a solution of pyridine (20 ml), under nitrogen at rt, was added successively **7a** (780 mg, 2.91 mmol), TEA (0.42 ml, 2.90 mmol), DMAP (17 mg, 0.145 mmol) and **6** (200 mg, 0.065 mmol). After 36 h of stirring at rt, the mixture was evaporated and extracted with CH_2Cl_2 and H_2O. The organic layer was concentrated under vacuum and purified through a Sephadex LH20 cartridge to give after evaporation of CH_2Cl_2 **8a** as red solid (325 mg, 97%). Data for **8a**: MS (ESI): $[M+H]^+=5154.64^+$; (c) Suzuki coupling, ex. **9a**: To a solu-

tion of DMF (10 ml) were added, under nitrogen, **8a** (0.142 g, 0.027 mmol), Pd $(PPh_3)_4$ (0.014 g, 0.012 mmol), 2-formylphenylboronic acid (0.074 g, 0.496 mmol) and Na_2CO_3 (0.31 ml, 2 M in H_2O). The mixture was heated at 110°C for one night and extracted with AcOEt and H_2O. The organic layer was evaporated and purified through a Sephadex LH20 cartridge with CH_2Cl_2 to yield **9a** as red solid (0.11 g, 82%). Data for **9a**: MS (FAB): $[M+H]^+ = 4959.3^+$; (d) Cleavage procedure, ex. **11a**: To a mixture of TFA/CH_2Cl_2 (20:80, 10 ml) was added **9a** (0.090 g, 0.018 mmol) under nitrogen. After 1 h at rt, the solvent was evaporated, the residue was taken up with a mixture of MeOH/CH_2Cl_2 (60:40, 10 ml), treated with K_2CO_3 (0.09 g, 0653 mmol) overnight. The mixture was then extracted with CH_2Cl_2 and NaOH (1N), the insoluble red dendrimer was filtered, the aqueous layer was washed with CH_2Cl_2, acidified with HCl (1N), and re-extracted with AcOEt. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give **11a** as a white solid (0.018 g, 50%). Data for **11a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30 (br d, $J = 7.5$ Hz, 1H), 7.34 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, 1H), 7.56 (m, 2H), 7.65 (td, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, 1H), 7.69 (td, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, 1H), 7.89 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, 1H), 7.95 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, 1H), 9.71 (s, 1H), 12.82 (br s, 1H); MS (FAB): $[M-H]^- = 225^-$.