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Efficient Multigram Synthesis of the Repeating Unit of Gallic Acid-Triethylene Glycol Dendrimers

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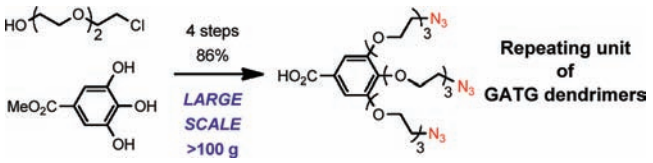
ABSTRACT



A multigram synthesis of the repeating unit of GATG (gallic acid-triethylene glycol) dendrimers is described through an efficient and cost-effective route. These conditions overcome major problems precluding scaling up and afford product in excellent overall yield and purity. Special attention has been paid in this process to green chemistry principles: atom economy, safety, and waste reduction. This scheme could be easily adapted for the preparation of similar dendritic systems.

Dendrimers are synthetic tree-like macromolecules composed of repetitive layers of branching units that are prepared in a controlled iterative fashion, through generations with discrete properties. They are characterized by well-defined structures, nil dispersity, and a globular morphology in the nanometre scale.[1] These characteristics have rendered dendrimers with applications in a plethora of fields, including catalysis and materials science.[2] In addition, the inherent multivalency of dendrimers allows for the controlled display of specific ligands, drugs, and targeting and imaging agents.[3]

During the past decade, great efforts have been devoted to the development of more efficient synthetic methodologies for the facile preparation and functionalization of dendrimers,[4] a fact that has been fueled by the rapid adoption of the Sharpless' click concept[5] in this field.[6]

GATG (gallic acid-triethylene glycol) is an emergent family of dendrimers that are prepared divergently from repeating unit **1** (Figure 1). GATG sialodendrimers and dendronized chitosans up to the second generation (G2) were initially described by the group of Roy as potential microbicides.[7] Despite this interesting application, the preparation of repeating unit **1** (four steps from triethylene

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glycol, 23%)[7] proved to be a hurdle in accessing large quantities of GATG dendrimers and to higher generations.

Aware of these limitations, in 2006 our research group successfully reported an improved synthetic route to **1** from commercially available chlorotriethylene glycol **2** (77% overall yield, Scheme 1 in black) which has paved the way for the preparation of GATG dendrimers and their block copolymers with poly(ethylene glycol) (PEG) in larger quantities and up to G4.[8−10] The functionalization of these dendrimers by means of the Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC)[11] has been straightforward in our hands.[8−13] The resulting functionalized dendrimers have emerged as interesting tools in the study of the multivalent carbohydrate−receptor interaction, the dynamics of dendrimers, and the preparation of polyion complex micelles and dendriplexes for gene therapy.[10,12] More recently, we have developed GATG dendritic contrast agents for MRI and as inhibitors of the dimerization of the capsid protein (CA) of HIV-1.[13] In another example, the group of Kinbara and Aida has described a guanidinated GATG dendrimer of G2 as a molecular glue with the ability to stabilize microtubules and to inhibit the sliding motion of actomyosin.[14]

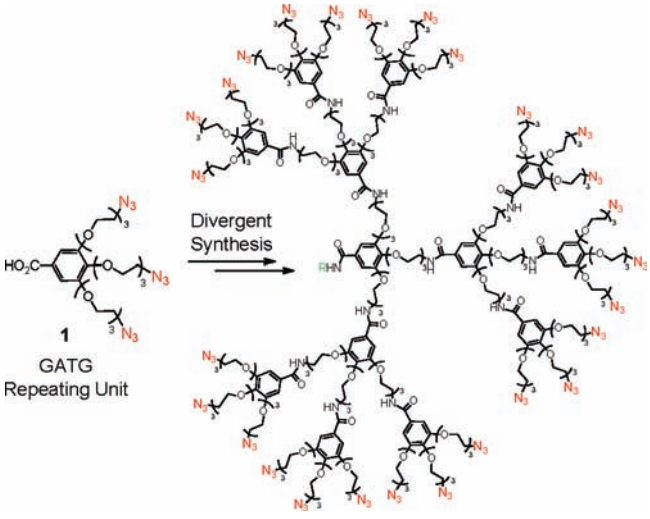

Figure 1. Repeating unit and third generation GATG dendrimer.

These novel applications of GATG dendrimers render the large scale preparation of **1** of great interest. However, attempts to scale up the synthesis shown in Scheme 1 (in black)[8] to batches larger than 8 g were unfortunately troublesome due to laborious chromatographic purifications of **5** and **7**, which finally resulted in lower yields and unfeasibility. Herein, we report a multigram synthesis based on green chemistry principles (atom economy, safety, waste reduction)[15] which affords batches of **1** larger than 100 g in an excellent overall yield and purity (Scheme 1, in blue). Key points for this synthesis are (i) a safer preparation of **3** by lowering the temperature of the reaction and the use of H_2O as solvent; (ii) the replacement of tosylate **5** by chloride **4**, which is efficiently prepared in a solventless process and purified by nonchromatographic means, providing a more atom-economical production of **7**; and (iii) a general reduction of waste generated.

The synthesis of **1** starts with the substitution of a chloride for an azide group in **2** (NaN_3). As seen in Scheme 1 and Table 1 (entry 1), this process traditionally required high temperatures (100 °C) and the use of DMF as solvent (0.25 M).[8] In spite of the relative thermal stability of NaN_3 and **3** (see the Supporting Information, SI), we decided to improve the safety of this step for multigram synthesis by performing the reaction under milder conditions. Thus, a set of experiments were designed to reduce the temperature of the reaction. As seen in Table 1, although lowering the temperature from 100 to 85 °C had no effect on yield (entry 2), a further reduction to 75 °C led to incomplete conversions (entry 3). This could be overcome by increasing the concentration from the original 0.25 to 1 M (entry 4), which also presents the advantage of reducing the amount of solvent used. Indeed, solvents account for the vast majority of

Table 1. Optimized Conditions for the Synthesis of **3**

entry[a]	scale (g)	additive (equiv)	concn (M)	solvent	temp (°C)	time (h)	yield (%)[b]
1	0.1	–	0.25	DMF	100	12	100
2	0.1	–	0.25	DMF	85	12	100
3	0.1	–	0.25	DMF	75	12	85
4	0.1	–	1	DMF	75	14	100
5	0.1	–	1	H_2O	75	44	100
6	0.1	–	2	H_2O	75	32	100
7	0.1	NaI (0.1)	2	H_2O	75	32	100
8	150	–	2	H_2O	75	48	100

[a] In all cases 2 equiv of NaN_3 were used. [b] Yields refer to conversions determined by ^1H NMR (D_2O), except entry 8.

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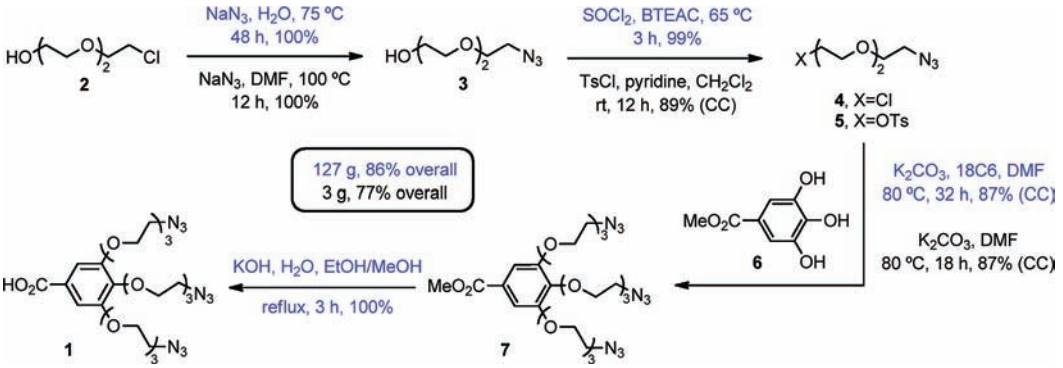
Scheme 1. Synthetic Route for the Multigram Preparation of the GATG Repeating Unit (**1**) (in blue) Compared to Previously Reported Conditions (in black; refs 7,8); CC Refers to Column Chromatography



mass wasted in synthesis, which has forced chemists to consider greener alternatives.[15,16] In this respect, H_2O, the only natural solvent on earth, is recognized as a safe, nontoxic, nonflammable, environmentally benign, and inexpensive alternative with great potential for large scale processes (high heat capacity and convenient boiling point-).[5,15,16] Accordingly, we decided to explore the use of H_2O as solvent for the conversion of **2** to **3**. Application to H_2O of the best conditions encountered for DMF (Table 1, entry 4) revealed slower reaction rates,[17] which could be efficiently counterbalanced with slightly longer reaction times and higher concentrations (Table 1, entries 5–6). No accelerating effect was observed when using NaI as a catalyst (entry 7). Conditions in entry 6 proved to be easily scalable, affording **3** quantitatively in 158 g scale (entry 8). Upon completion of the reaction, the mixture was cooled down to rt and H_2O was removed under reduced pressure. The resulting residue was suspended in Et_2O and solids (NaN_3 and NaCl) filtered through a sintered funnel. Our previously described use of CH_2Cl_2 and Celite for this filtration[8] is discouraged for large scale synthesis to avoid formation of diazidomethane or other potentially explosive compounds by NaN_3 in contact with traces of heavy metals in Celite (see the SI).[18]

With a method in hand for the multigram preparation of azidoalcohol **3**, we faced the incorporation of the chloride group in **4**. With this aim, thionyl chloride ($SOCl_2$) was selected as a chlorinating agent based on its easy removal by distillation. In addition, the volatility of HCl and SO_2 produced in the process simplifies purifications. Initial studies were performed with pyridine/DMAP in different solvents (CH_2Cl_2, $CHCl_3$, toluene) and temperatures (rt–100 °C), which unfortunately led to **4** in moderate yields (Table 2, entries 1–4). We then explored the possibility of using neat $SOCl_2$ in a solventless process. These conditions were envisioned as more convenient than those for entries 1–4 and our previously reported process (TsCl, pyridine–CH_2Cl_2).[8] In addition to a nonchromatographic purification and the avoidance of toxic solvents, a dramatic reduction in waste would result in agreement with the principle "the best solvent is no solvent".[15,16] Indeed, treatment of **3** with 2 equiv of $SOCl_2$ in the presence of catalytic amounts of benzyltriethylammonium chloride (BTEAC, 0.3 mol %)[19] afforded **4** quantitatively (1 h, 65 °C) after an aqueous workup to recover the catalyst (Table 2, entry 5). This transformation proved to be highly practical and scalable, allowing the production of **4** in 99% yield in amounts larger than 170 g (entry 6).

Table 2. Optimized Conditions for the Synthesis of **4**

entry[a]	scale (g)	additive	solvent	temp (°C)	time (h)	yield (%)
1	0.5	py	CH_2Cl_2	rt	48	49
2	0.5	py	$CHCl_3$	reflux	48	62
3	0.5	py	Toluene	100	48	59
4	0.5	DMAP	CH_2Cl_2	rt	48	64
5	1	BTEAC	–	65	1	100
6	160	BTEAC	–	65	3	99

[a] In all cases 2 equiv of $SOCl_2$ were used.

When a reaction between methyl gallate **6** and chloride **4** was performed under the conditions described for tosylate **5** (K_2CO_3, DMF, 80 °C; Scheme 1),[7,8] the lower reactivity of **4** was soon revealed, leading to **7** in a moderate 48% yield (Table 3, entry 1). As a result, a set of experiments were performed to study the effect of the concentration, temperature, solvent, amount of base, and catalysts [KI and 18-crown-6 (18C6)] on the kinetics and yield of the reaction. The influence of KI and 18C6 was analyzed first. The use of 0.1 equiv of each one resulted in conversions around 70% (Table 3, entry 2), which could be increased up to 93% at concentrations higher than the original 0.1 M

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(entry 3). The effect of the temperature was then analyzed, with temperatures lower than 80 °C resulting in much lower conversions, while higher temperatures resulted in partial decomposition (entries 4–5). The use of acetone as solvent or less than 10 equiv of K_2CO_3 was unsuccessful (entry 6). When analyzing the separate influence of KI and 18C6, a negligible effect of KI on reactivity was shown (entry 7). Finally, the scaling up of conditions in entry 7 gave us the opportunity to reduce the amount of added chloride **4** from 4 equiv to 3.06 (1.02 equiv per hydroxyl group in **6**), with no adverse effect on yield. This represents a savings of 23% in added **4** and ensures an easier purification of **7**. Workup conditions involved solvent evaporation followed by filtration through a pad of alumina to remove solid residues. Aqueous workup was left aside due to the partial solubility of **7** in H_2O. Purification of the crude product by automatic medium pressure liquid chromatography (MPLC) was revealed to be less time-consuming than conventional column chromatography, while affording **7** with higher purity. When these conditions were applied to 44 g of gallate **6**, 130 g of pure **7** were obtained in 87% yield (Table 3, entry 8; purification by MPLC: 5 portions, 30 min each portion).

Table 3. Optimized Conditions for the Synthesis of **7**

entry[a]	scale (g)	additive[b]	K_2CO_3 (equiv)	concn (M)	temp (°C)	time (h)	yield (%)[c]
1	0.15	–	10	0.1	80	24	48
2	0.15	KI, 18C6	10	0.1	80	24	72
3	0.15	KI, 18C6	10	0.5	80	24	93
4	0.15	KI, 18C6	10	0.5	70	24	58
5	0.15	KI, 18C6	10	0.5	60	24	32
6	0.15	KI, 18C6	6	0.5	80	24	85
7	0.15	18C6	10	0.5	80	24	93
8	130	18C6	10	0.5	80	32	87

[a] In all cases 4 equiv of **4** were used, except 3.06 equiv for entry 8. [b] 0.1 equiv of KI and 0.1 equiv of 18C6 were used. [c] Yields were determined by ^{1}H NMR ($CDCl_3$), except those for entries 1 and 8.

The final step in the preparation of **1** involves the hydrolysis of **7**. This was efficiently performed in a 130 g scale with aq KOH (2.2 equiv) in boiling methanol. After neutralization with Amberlite IR-120, acid **1** was obtained quantitatively (Scheme 1). Similar results were obtained by using EtOH as a cosolvent, or at rt with a 2-fold concentration of KOH. Interestingly, these conditions represent a 5 times reduction in the amount of organic cosolvent compared to previous conditions.[7,8] When acidification was performed with aq HCl instead of Amberlite IR-120, lower mass recoveries (around 70%) were typically obtained by extraction.

In conclusion, conditions for the multigram preparation of the repeating unit of GATG dendrimers (**1**) have been developed that afford batches larger than 100 g in excellent overall yield and purity (4 steps, 86%, one chromatographic step). Special attention has been paid in this process to observe green chemistry principles: atom economy, safety, and waste reduction. This scheme could be easily adapted for the multigram preparation of similar systems with varying numbers and lengths of spacer arms and interesting building blocks for the construction of functional nanostructures.[20]

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Supporting Information Available. Materials and methods, WARNING notice on azides, experimental procedures, characterization, and spectra of **1**, **3**, **4**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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