A convergent synthesis of heterocyclic dendrimers using the 1,3-dipolar cycloaddition reaction of organic azides and acetylenedicarboxylate esters

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Dendrimers containing 1,2,3-triazole rings were prepared by using the 1,3-dipolar cycloaddition reaction of organic azides and acetylenedicarboxylic esters.

Dendrimers are highly branched macromolecules, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies.[1] Ideally, the reactions employed are high yielding, without isomerizations or side reactions occurring. This then allows one to obtain defined, uniform structures. Well known processes, such as the Michael reaction, Williamson ether synthesis, amidations and reductions have been used extensively in pioneering work by Vögtle, Tomalia, Fréchet and Newkome. During the last decade, more sophisticated reactions were also employed. This allows a large structural and functional variation. Dendrimers with heterocyclic subunits are relatively rare, although heterocycles are a very important class of organic compounds. Most of the dendrimers with heterocyclic loci[2] are from the (oligo)pyridine type. Oxadiazole dendrimers have been described independently both by Strohriegl *et al.*[3] and Kraft.[4] The oxadiazole ring was formed by condensation of acid chlorides and tetrazoles.

Another important way of forming heterocyclic five membered rings is by 1,3-dipolar cycloaddition. The required 1,3-dipoles generally are very reactive and are mostly generated *in situ* (*e.g.* nitrile oxides or nitrile imines) or kept only for short times (*e.g.* diazoalkyl compounds). Azides are among the most stable 1,3-dipoles and generally can be stored for indefinite time without significant decomposition. Thus, they would be well suited for the synthesis of dendrimers. It is interesting to note that Fréchet used a dendritic benzyl azide in an insertion reaction of C_{60}.[5] Other cycloadditions that have been used by Wiester and Müllen are the Diels–Alder cycloadditions of cyclopentadienones, leading to shape-persistent dendrimers.[6]

We used a convergent approach, connecting the Fréchet dendrons[7] to the acetylenedicarboxylate, and combining the functionalized dipolarophile with a polyazide core. This then gives dendrimers of high molecular weight containing 1,2,3-triazoles as the connecting functions. Because of the high local density of nitrogen atoms, these macromolecules could be useful for the complexation of metal ions.

The polyazide core reagents **1** and **2** were prepared in high yield from the known[8] polybromides **3** and **4** by nucleophilic substitution with azide anion. Compounds **1** and **2** are stable compounds, which were described in the specialized literature[9] to be relatively insensitive to heat or shock (Scheme 1).

To test the effectiveness of the 1,3-dipolar cycloaddition reactions of these polyazides and acetylene dicarboxylates, we have reacted **1** and **2** with the commercial dimethyl and di-*tert*-butyl acetylenedicarboxylate **5** and **6**. The cycloadducts **13**–**16**, which
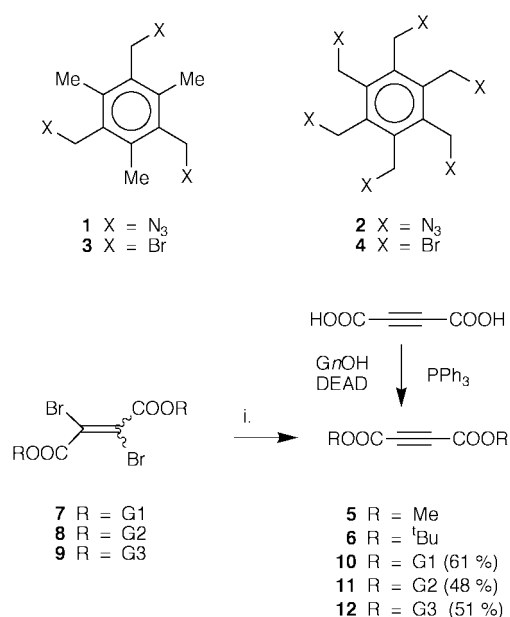
Scheme 1 *Reagents and conditions*: i, Zn, I_2 (trace), THF, reflux.

can be seen as zeroth generation dendrimers were obtained in good to excellent yield (Schemes 1 and 2). The reaction can be monitored by IR spectroscopy by following the disappearance of the N_3 stretching band around 2100 cm^{-1}. This band is always very strong, and thus we have an excellent tool to detect even traces of remaining unreacted azide functions. The cycloadducts **13** and **14** (R = methyl) can be made water-soluble by saponification of their ester functions. Upon treatment of the corresponding polycarboxylates with dilute acid the corresponding polyacids **17** and **18** (R = H) were precipitated from the water solution.

For the synthesis of higher generations of dendrimeric cycloadducts we needed an efficient synthesis of the acetylenedicarboxylate esters **10**, **11** and **12** (R = G1, G2 and G3 respectively). Adapting a literature procedure,[10] we used the Mitsunobu esterification of 2,3-dibromomaleic acid or 2,3-dibromofumaric acid with the Fréchet dendritic wedges of the first to third generation. The esters were then deprotected using activated zinc. Generally, the dibromofumarates afforded the best results, whereas the dibromomaleates gave partially debrominated side-products, which are difficult to separate from the acetylenedicarboxylates. Alternatively, we used the Mitsunobu esterification of acetylenedicarboxylic acid with the Fréchet benzyl alcohols. The yields of the latter reactions
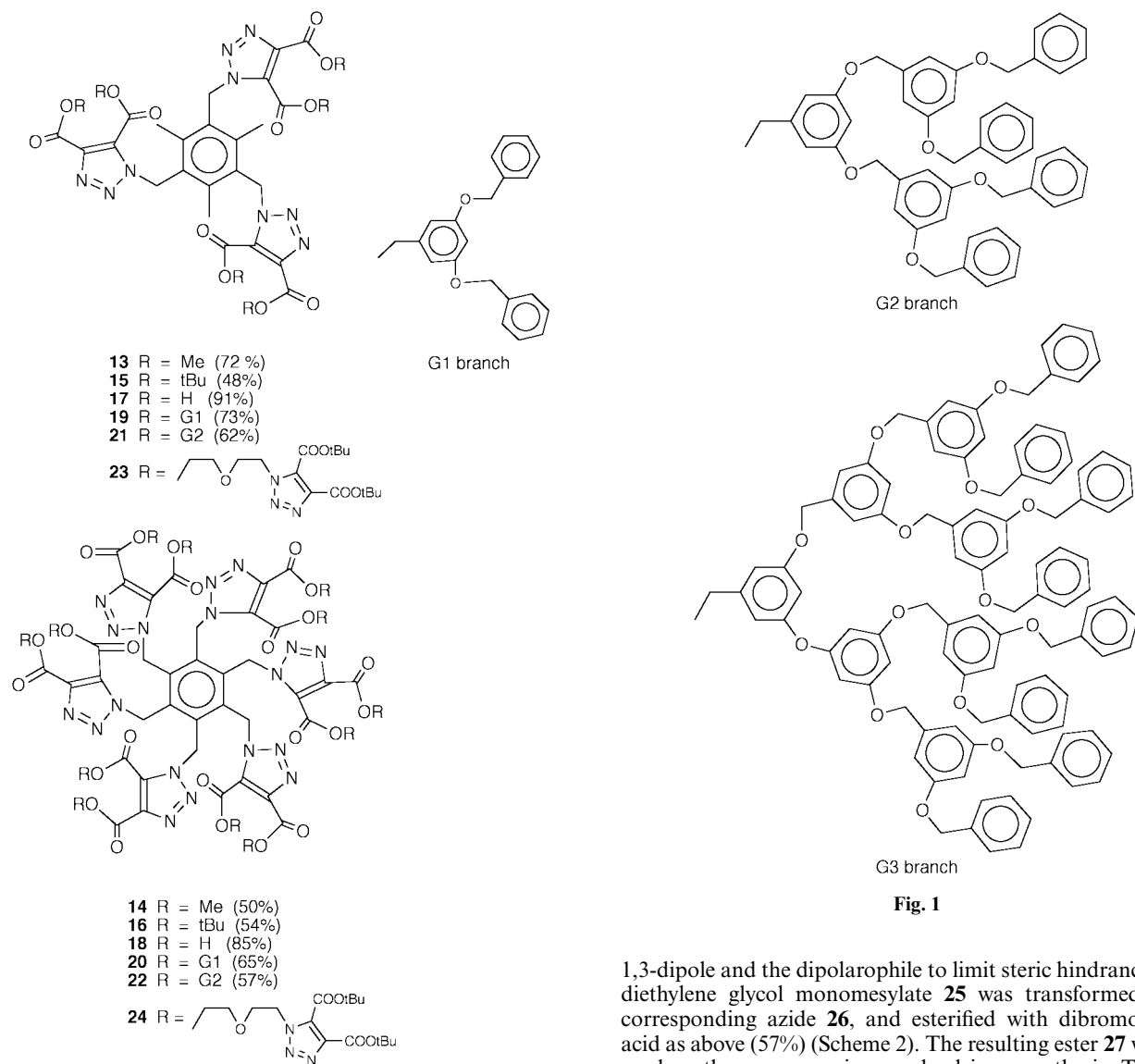
13 R = Me (72 %)
15 R = tBu (48%)
17 R = H (91%)
19 R = G1 (73%)
21 R = G2 (62%)

23 R = [structure with COOtBu groups]

G1 branch

14 R = Me (50%)
16 R = tBu (54%)
18 R = H (85%)
20 R = G1 (65%)
22 R = G2 (57%)

24 R = [structure with COOtBu groups]

G2 branch

G3 branch

Fig. 1

generally are lower (20–40%) than the yields following the dibromofumarate route (Scheme 1, Fig. 1).

A slight excess (1.1 equiv. per azide function) of the acetylenedicarboxylate dendrimers **10–12** was heated for several days in toluene at 70 °C in the presence of the core reagents **1** and **2**. The reaction was followed by IR spectroscopy until the azide band had disappeared or no longer changed in intensity. After chromatographic separation, the dendrimers **19–22** (R = G1 and G2) were obtained in yields comparable to those of the model compounds. The large shift of the azide/triazole methylene group (δ 4.53–4.64 for **1**, **2** to 5.50–6.02 ppm for **19–22**) is diagnostic for the formation of the triazole ring. The ^{1}H and ^{13}C NMR spectra reflect the high molecular symmetry in these dendrimers. Furthermore, the dendrimers **19** (m/z 2466 for [M + Na]$^+$) , **20** (m/z 4721 for M$^+$), and **21** (m/z 5037 for M$^+$) were characterized by MALDI TOF spectrometry.

However, the acetylene G3 dendron **12** failed to add completely to both cores **1** and **2**, even after prolonged heating, as was evident from the IR spectra (N$_3$ stretching band remaining at 2096 cm^{-1}). The products from these attempts were isolated, analyzed by ^{1}H NMR spectroscopy, and found to be unsymmetrically substituted with both triazole and azide functions present (ratio of the methylene integrations respectively 2:1 in both cases). Clearly the cycloaddition reaction is sterically hindered at higher generations.

In a next step, we wanted to introduce several levels of 1,2,3-triazoles in the dendrimer structure. Again, we used dibromofumarate as the protected form of acetylenedicarboxylate. We decided to place flexible diethylene glycol spacers between the

1,3-dipole and the dipolarophile to limit steric hindrance. Thus, diethylene glycol monomesylate **25** was transformed to the corresponding azide **26**, and esterified with dibromofumaric acid as above (57%) (Scheme 2). The resulting ester **27** was then used as the monomer in our dendrimer synthesis. Thus, the azide functions of **27** were reacted with **6** to give a first generation dibromofumarate **28** (71%), which was converted to the acetylenedicarboxylate **29** in 94% yield. The cores **1** and **2** reacted with **29** to give the second generation dendrimers **23** and **24** in 57 and 44% isolated yields, respectively. A more extended hexaazide core **30**, prepared from tribromide **3** and 3,5-bis(azidomethyl)phenol reacted with **29** to give a slightly improved yield (54%) of the dendrimer **31**, which still means more than 90% yield per cycloaddition reaction. Because of the presence of the peripheral *tert*-butyl groups, the polytriazole dendrimers **23**, **24** and **31** have excellent solubilities, for instance in chlorinated solvents. They were purified by chromatography. Again, the dendrimers **23**, **24** and **31** were characterized by ^{1}H and ^{13}C NMR spectroscopy.[11]

The second generation dibromofumarate **32** was prepared (70%) from monomer **27** and the first generation acetylene **29** (Scheme 3). Unfortunately, we have so far not succeeded in reducing this compound to the corresponding acetylenedicarboxylate. At this point, the number of generations seems to be limited by the method of protection/deprotection of the acetylenedicarboxylate, rather than by the effectiveness of the 1,3-dipolar cycloaddition of the azides.

Further studies are under way to explore the potential of the 1,3-dipolar cycloaddition of azides in dendrimer chemistry.

Acknowledgements

Scheme 2 *Reagents and conditions*: i, NaN₃, acetonitrile, reflux; ii, dibromofumaric acid, THF, DEAD, PPh₃; iii, toluene, acetylenedicarboxylate ester, azide, reflux; iv, Zn, I₂ (trace), THF, reflux.

Scheme 3 *Reactions and conditions*: i, toluene, reflux.

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11 General procedure for the cycloaddition, applied to dendrimer **22**: a solution of hexakis azide **2** (0.06 mmol, 23 mg) and 6.6 equivalents of the G2 acetylene **11** (0.40 mmol, 0.6 g) was refluxed in toluene (3 ml) during 7 d (IR monitoring of the azide band). The solvent was removed and the residue was chromatographed over silica gel with dichloromethane as the eluent. This afforded dendrimer **22** (0.41 g, 57%) as a glass. IR (KBr, cm^{-1}) 1734 (CO); ^{1}H NMR (CDCl$_3$, 400 MHz) δ = 4.62 (s, 48H, CH$_2$O), 4.76 (2s, 96H, CH$_2$O), 5.25 (2s, 24H, CH$_2$O), 5.90 (br s, 12H, CH$_2$N), 6.27–6.60 (m, 108H, C$_6$H$_3$), 7.09–7.28 (m, 240H, Ph); ^{13}C NMR (CDCl$_3$, 100 MHz) δ = 49.22 (CH$_2$N), 67.05, 68.48, 69.68, 69.83, 69.87 (CH$_2$O), 101.56, 101.99, 102.42, 106.35, 106.40, 106.60 (C$_6$H$_3$CH), 127.44, 127.46, 127.76, 127.79, 128.39, 128.49 (Ph), 129.02 (triazole C5), 136.56, 136.82, 136.86, 137.43 (*ipso* CH$_2$-C Ar), 139.24, 139.27 (*ipso* CH$_2$-C Ar), 140.48 (triazole C4), 158.27, 159.63 (C=O), 159.85, 159.90, 160.0 (*ipso* C–O Ar). Analysis calc. for C$_{624}$H$_{528}$N$_{18}$O$_{96}$: C 76.4%, H 5.4%, N 2.6%. Found C 76.1%, H 5.2%, N 2.7%.