A Nonisocyanate Route to Monodisperse Branched Polyurethanes

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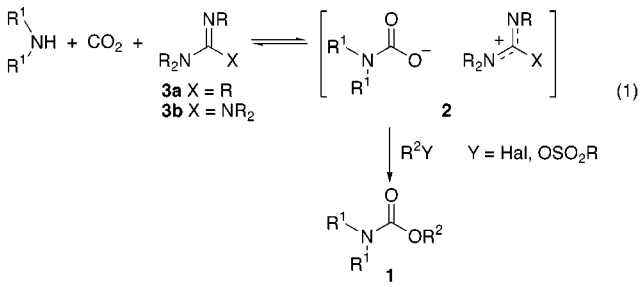
Received August 30, 2001

Introduction

The chemistry of dendrimers has attracted an astonishing amount of attention in recent years.[1] Yet, despite the widespread use of conventional polyurethanes,[2] the chemistry of dendritic polyurethanes remains little explored. There have been reports of hyperbranched polyurethanes,[3] but the use of the urethane functional group to construct monodisperse dendrimers is limited to isolated examples.[4] The explanation for the surprisingly slow development of polyurethane dendrimers may lie in the fact that most dendrimers are [*n*]-polymers, being constructed from AB_n units,[1] whereas linear polyurethanes are traditionally [*m*,*n*]-polymers, prepared from reaction of AA and BB monomers (diisocyanates and diols).[2] Indeed, only very recently was a general method for [*n*]-polyurethane synthesis reported.[5] Therefore, the direct application of traditional polyurethane methodology to dendrimer synthesis has not been possible.

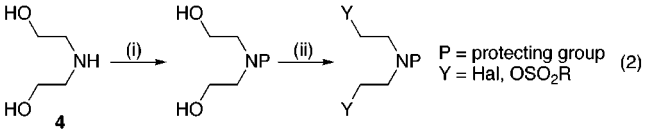
Although it is not inconceivable that isocyanate technology could be adapted to dendrimer synthesis, account must be taken, when developing new methodology, of the environmental impact of the process. Isocyanates are toxic intermediates and their preparation from amines more often than not involves the use of phosgene, which is also highly toxic, or synthetic equivalents prepared from phosgene.[6] We aimed to develop a nonisocyanate route to monodisperse dendritic polyurethanes.

We were attracted to a method developed for the synthesis of urethanes **1** from amines, carbon dioxide, and electrophiles such as alkyl halides or alkyl sulfonates (eq 1).[7] Amines react readily with carbon dioxide in the presence of base to form carbamate anions **2**. Although these anions are usually poor nucleophiles, it is possible to significantly increase their nucleophilicity if the positive charge on the counterion is delocalized, thus reducing ion-pairing and leading to a "naked" anion. This is best achieved by the use of amidine **3a** or, better still, guanidine **3b** bases.[7] Since the latter are not commercially available, we restricted ourselves to the use of an amidine, diazabicycloundecene (DBU), in this study.



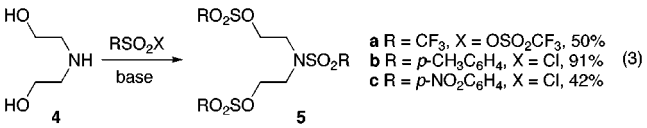
(1)

Our strategy was based on readily available diethanolamine **4** as the branch unit. The proposed convergent synthesis required (i) protection of the secondary amine and (ii) activation of the alcohol groups to nucleophilic attack, by conversion to halides or sulfonates (eq 2).



(2)

While there are a number of ways in which this could be achieved in two steps, we realized that sulfonate groups could be installed as both *N*-protecting groups and *O*-activating groups in one step (eq 3). The success of this strategy, using diethylamine as a model terminal group, is described herein.



(3)

Results and Discussion

We first prepared the tris(trifluomethanesulfonyl) derivative **5a** of diethanolamine. The tritosyl analogue **5b** was also synthesized since it was expected to exhibit complimentary reactivity. The less electron-withdrawing tosyl group renders the sulfonates poorer leaving groups but the same property means that the N−S bond is weaker than in the triflamide, hence deprotection of tosylamides should in principle be easier.

To begin the dendrimer synthesis, diethylamine was dissolved in acetonitrile in a small glass autoclave and subjected to 40 psi pressure of carbon dioxide. An acetonitrile solution of the trisulfonyl diethanolamine **5** was added, with the pressure being maintained. Both **5a** and **5b** reacted smoothly to give the *N*-protected diurethanes **6**, with the triflamide **6a** being formed in a higher yield, as expected (eq 4). However, neither the triflamide

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(3) Spindler, R.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 4809; Kumar, A.; Ramakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1453.

(4) Taylor, R. T.; Puapaiboon, U. *Tetrahedron Lett.* **1998**, *39*, 8005; Rannard, S. P.; Davis, N. J. *Org. Lett.* **2000**, *2*, 2117; dendrimers have also been functionalised as carbamates, for example Spindler, R.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 913.

(5) Versteegen, R. M.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2917.

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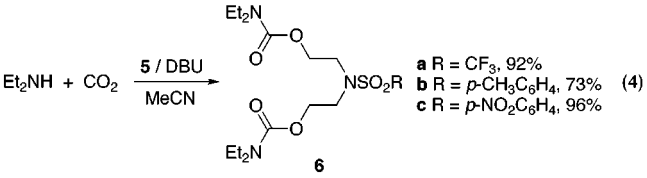
(7) McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820; Yoshida, Y.; Ishii, S.; Watanabe, M.; Yamashita, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1534.

10.1021/jo016075i CCC: $20.00
Published on Web 11/15/2001



(4)

nor the tosylamide could be deprotected using the usual metal-mediated reductive methods.[8]

As we were unable to deprotect either the triflamide or the tosylamide, we turned to the 4-nitrophenylsulfonyl (nosyl) group, sulfonamides of which are readily cleaved by reaction with thiophenol in a nucleophilic aromatic substitution process.[9] The trinosyl derivative **5c** of diethanolamine proved simple to prepare and also reacted readily with the carbamate anion derived from diethylamine and carbon dioxide (eq 4).

Pleasingly, deprotection of the nosylamide **6c** was high-yielding (Scheme 1), and the product was simple to separate from the sulfide byproduct **8** using column chromatography. To prove the method was applicable to dendrimer synthesis, we needed to show that the deprotected amine **7** could be further reacted to produce a higher generation dendron **9** and also that it could be coupled to a "core" molecule **10** to produce a small dendrimer **11**. Both these reactions, as shown in Scheme 1, were trouble free.

Conclusion

In conclusion, an approach to dendritic polyurethanes has been developed that has three main advantages. First, cheap, nontoxic carbon dioxide is used as an alternative to toxic phosgene or reagents derived from it. Second, commercially available diethanolamine is used as the branch unit. Finally, the chemistry of the nosyl group permits simultaneous activation of alcohols and protection of amines, thus simplifying the syntheses.

Experimental Section

Carbon dioxide was supplied from BOC GASES Ltd. and used without any further purification. The carbon dioxide reactions were performed in a glass and PTFE pressure vessel manufactured by Ken Kimble (Reactor Vessels) Ltd. rated to 10 bar at 100 °C or 6 bar at 150 °C with a capacity of 250 mL. For safety reasons, this pressure vessel was equipped with a bursting disk. The bursting pressure of the reactor was a multiple of the maximum allowable working conditions. The glass pressure tube was mounted in a protective cage. If, during the reaction, stirring was required, a PTFE coated magnetic stirring bead was placed in the vessel to allow agitation via a magnetic stirrer. The miniclave was sealed by the PTFE coverplate, with a Viton O-ring being clamped to the vessel using a stainless steel threaded clamp. The complete miniclave was heated or cooled by placing it in a temperature-controlled bath. Heating and stirring were performed simultaneously by using a bath on a magnetic hotplate. Pressure and temperature were monitored using the pressure gauge and a thermometer mounted in the thermopocket on the coverplate. Carbon dioxide was dosed or vented via the needle valve also mounted on the coverplate.

***N,N*-Bis-(2-*p*-nitrobenzenesulfonyloxyethyl)-*N*-*p*-nitrobenzenesulfonamide 5c.** To diethanolamine (4.00 g, 38.1 mmol) in dichloromethane (150 mL) were added triethylamine (17.5 mL, 125.7 mmol) and a few drops of (dimethylamino)-pyridine. The solution was stirred at 0 °C for 30 min under a stream of dry nitrogen. From a pressure equalizing dropping funnel *p*-nitrobenzesulfonyl chloride (27.86 g, 125.7 mmol) in dichloromethane (75 mL) was added dropwise. The reaction mixture was left stirring for 1 h. The product precipitated and was collected by filtration. The solid was recrystallized from dichloromethane to yield light yellow crystals[10] of **5c** (21.3 g, 42%); mp 76−79 °C (CH_2Cl_2), (found: C, 35.46; H, 2.85; N, 7.06; $(C_{22}H_{20}O_{14}N_4S_3)_5(CH_2Cl_2)_8$[10] requires C, 35.58; H, 2.93; N, 7.03); ν_{max}/cm^{-1} 1609 (C=C st.), 1520 (NO_2 st.); ^1H (250 MHz, [$^2H_6$]-DMSO), 3.49 (4 H, t, *J* 5), 4.17 (4 H, t, *J* 5), 8.02 (2 H, AA′ of AA′BB′ *J* 8), 8.08 (4 H, AA′ of AA′BB′, *J* 8), 8.27 (2 H, BB′ of AA′BB′, *J* 8), 8.42 (4 H, BB′ of AA′BB′, *J* 8); ^{13}C (100 MHz, [$^2H_6$]-DMSO) 48.51, 69.91, 125.41, 125.66, 129.64, 130.38, 141.78, 145.21, 151.29, 152.03; *m*/*z* (FAB, 70 meV) 661.0219 (MH^+ requires 661.0216).

***N,N*-Bis-(2-diethylcarbamoyloxyethyl)-*N*-*p*-nitrobenzenesulfonamide 6c.** A solution of diethylamine (3.32 g, 45.4 mmol) and DBU (6.91 g, 45.4 mmol) in acetonitrile (100 mL) in a pressure vessel fitted with a pressure equalizing funnel was put under 40 psi CO_2 pressure. Addition of CO_2 resulted in a rise of temperature to ca. 40 °C. The solution was stirred for 1 h. A solution of trinosyl compound **5c** (10.00 g, 7.50 mmol)[10] in acetonitrile (20 mL) was added dropwise. The reaction mixture was warmed overnight at 80 °C. The pressure was released and the acetonitrile was evaporated in a rotary evaporator. The crude material was dissolved in ethyl acetate and washed with 0.5 M HCl solution, water, and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated in a rotary evaporator to dryness to give **6c** as a dark brown oil (3.55 g, 96%). ν_{max}/cm^{-1} 1693 (C=O st.), 1607 (C=C st.), 1531 (NO_2 st. as.); ^1H (250 MHz, $CDCl_3$) 1.09 (12 H, s br.), 3.22 (8 H, m br.), 3.54 (4 H, t, *J* 8), 4.22 (4 H, t, *J* 8) 8.02 (2 H, AA′ of AA′BB′, *J* 7), 8.35 (2 H, BB′ of AA′BB′, *J* 7); ^{13}C (100 MHz, $CDCl_3$) 13.37, 14.00, 41.23, 41.89, 47.79, 62.22, 124.47, 128.26, 145.70, 150.01; *m*/*z* (CI, 70 meV) 489.2033 (MH^+ requires 489.2019).

***N,N*-Bis-(2-diethylcarbamoyloxyethyl)amine 7.** To **6c** (5.00 g, 10.2 mmol) in DMF (100 mL) were added K_2CO_3 (2.83 g, 20.5 mmol) and PhSH (2.1 mL, 20.5 mmol). The reaction was stirred for 2 h at room temperature under a stream of dry nitrogen. The reaction mixture was filtered, and the DMF was removed by vacuum distillation. Flash chromatography on silica gel using 10% methanol:ethyl acetate (1:1) as an eluent gave **7** as a transparent oil (2.51 g, 81%). ν_{max}/cm^{-1} 1691 (C=O st.); ^1H (250 MHz, $CDCl_3$) 1.07 (12 H, t, *J* 7), 2.94 (4 H, t, *J* 5), 3.22 (8 H, m, *J* 7), 4.18 (4 H, t, *J* 5); ^{13}C (100 MHz, $CDCl_3$) 13.44, 14.05, 41.27, 41.85, 48.55, 64.14, 155.86; *m*/*z* (CI, 70 meV) 304.2230 (MH^+ requires 304.2236).

***N,N*-Bis-[*N*′,*N*′-bis-2-(2-diethylcarbamoyloxyethyl)carbamoyloxyethyl-*N*-*p*-nitrobenzenesulfonamide 9.** A mixture of amine **7** (4.00 g, 13.2 mmol) and DBU (1.99 g, 13.2 mmol) in acetonitrile (50 mL) in a pressure vessel fitted with a pressure equalizing funnel was put under 40 psi CO_2 pressure. Addition of CO_2 resulted in a rise of temperature to ca. 40 °C. The solution was stirred for 1 h. A solution of trinosyl compound **5c** (2.90 g, 2.20 mmol)[10] in acetonitrile (20 mL) was added dropwise. The reaction mixture was warmed overnight at 80 °C. After cooling to room temperature, the pressure was released and the acetonitrile was evaporated in a rotary evaporator. The reaction mixture was dissolved in ethyl acetate and washed with 0.5 M HCl solution, water, and brine. Flash chromatography on silica gel using methanol:ethyl acetate (1:9) as an eluent gave **9** as a dark brown oil (1.83 g, 88%); ν_{max}/cm^{-1} 1689 (C=O); ^1H (300 MHz, $CDCl_3$) 1.10 (24 H, m. br.), 3.20 (16 H, m. br.), 3.50 (12 H, m), 4.20 (12 H, m), 8.01 (2 H, AA′ of AA′BB′, *J* 8.9), 8.35 (2 H, BB′ of AA′BB′, *J* 8.9); ^{13}C (300 MHz, $CDCl_3$) 13.46, 14.05, 41.26, 41.86, 43.90, 47.14, 47.82, 62.58, 62.69, 63.03, 124.59, 128.38, 145.11, 150.16, 155.50, 155.56; *m*/*z* (CI, 70 meV) 949.4568 (MH^+ requires 949.4552).

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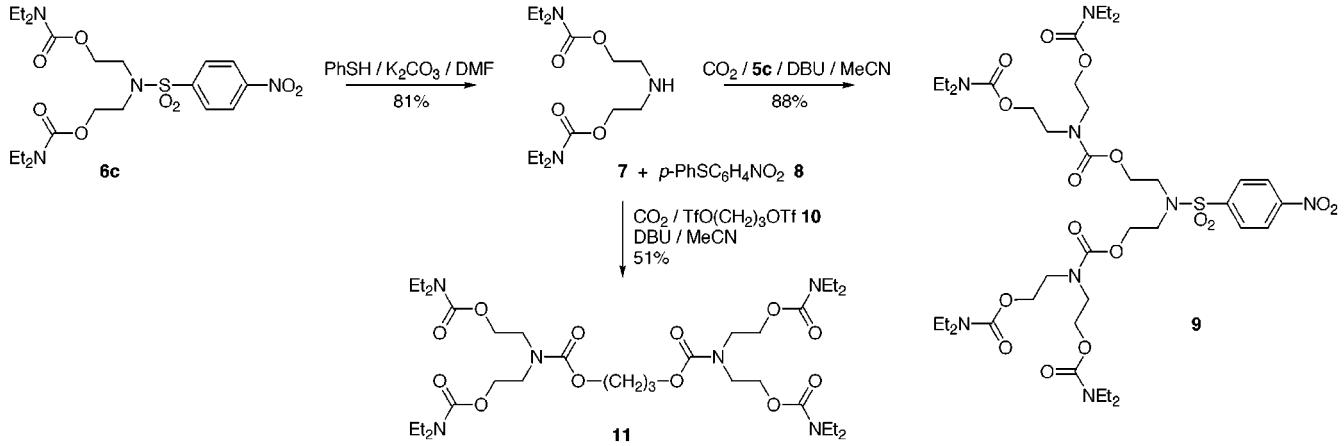
(9) Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(10) Combustion analysis of a number of independently prepared samples of **5c** consistently showed the presence of the same percentage of dichloromethane. That the solvent was included in the crystals was demonstrated by prolonged exposure to high vacuum, after which the correct amount of dichloromethane was still observed in the ^1H NMR spectrum. Since the syntheses of **6c** and **9** were completed before this fact had been confirmed, the amount of **5c** added was half that planned. This resulted in the other reagents inadvertently being used in greater molar excesses than intended.

Scheme 1



1,3-Bis(trifluoromethanesulfonyloxy)propane 10. To 1,3-propanediol (1.00 g, 13.1 mmol) in dichloromethane (100 mL) was added triethylamine (3.8 mL, 27.6 mmol). The solution was stirred at 0 °C under a stream of dry nitrogen for 10 min. Trifluoromethanesulfonic anhydride (4.6 mL, 27.6 mmol) in dichloromethane (50 mL) was added dropwise. The reaction was left stirring for 1 h. The reaction mixture was washed with water and brine, the organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Product **10** was obtained as a dark liquid (2.10 g, 47%); (found: C, 17.93; H, 2.18; $C_5H_6F_6O_6S_2$ requires C, 17.65; H, 1.78); ν_{max}/cm^{-1} 1203 (SO_2 st. as.), 1023 (SO_2 st. s.); ^1H (300 MHz, $CDCl_3$) 2.37 (2 H, t, *J* 5.8), 4.68 (4 H, t, *J* 5.8); ^{13}C (75 MHz, $CDCl_3$) 29.68, 71.82, 118.94 (q, *J* 319); *m*/*z* (70 meV), 358 (MNH_4^+, 80%).

1,3-*N*,*N*-Bis-[*N*′,*N*′-bis-(2-diethylcarbamoyloxyethyl)]-carbamoyloxypropane 11. A solution of secondary amine **7** (0.50 g, 1.65 mmol) and DBU (0.25 g, 1.65 mmol) in acetonitrile (50 mL) in a pressure vessel fitted with a pressure equalizing funnel was put under 40 psi CO_2. Addition of CO_2 resulted in a rise of temperature to ca. 40 °C. The reaction mixture was stirred for 30 min. A solution of 1,3-bis-(trifluoromethanesulfonyloxy)-propane **10** (0.26 g, 0.75 mmol) in acetonitrile (25 mL) was added dropwise. The reaction was left stirring for 1 h. Pressure was released and the acetonitrile evaporated in a rotary evaporator. The crude reaction mixture was dissolved in ethyl acetate and washed with 0.5 M HCl solution, water and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated in a rotary evaporator to yield **11** as an orange oil (0.28 g, 51%). ν_{max}/cm^{-1} 1694 (br., C═O st.); ^1H (300 MHz, $CDCl_3$) 1.11 (24 H, t br., *J* 5), 2.00 (2 H, m. br., *J* 5), 3.27 (16 H, m. br., *J* 5), 3.57 (8 H, m. br., *J* 5), 4.16 (8 H, m. br., *J* 5), 4.30 (4 H, m. br., *J* 5); ^{13}C (75 MHz, $CDCl_3$) 13.21, 13.78, 28.56, 41.00, 41.59, 46.66, 47.14, 58.45, 62.13, 62.54, 155.25, 155.71; *m*/*z* (CI, 70 meV), 735.4514 (MH^+ requires 735.4504, 1%).

Acknowledgment. We thank Claudio Di Lullo, Peter Jones and Ian Wood of Akzo Nobel and Steven Rannard and Nicola Davis of Courtaulds Coatings for their contributions and thank Akzo Nobel for financial support.

Supporting Information Available: Full experimental procedures and spectral characterization data for the compounds described above. Additionally, full experimental procedures and spectral characterization data for triflates **5a** and **6a** and tosylates **5b** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016075I