Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 7726–7730
Tetrahedron Letters

Direct selective reductive amination of carbonyl telechelic oligoisoprenes: elaboration of promising tri- and tetrafunctionalized oligoisoprene intermediates

Gaëlle Morandi, Nasreddine Kebir, Irène Campistron, Frédéric Gohier, Albert Laguerre and Jean-François Pilard*

Unité de Chimie Organique Moléculaire et Macromoléculaire, UCO2M, UMR CNRS 6011, Faculté des Sciences et Techniques, Université du Maine, Avenue Olivier Messiaen, F-72085 Le Mans cedex 9, France

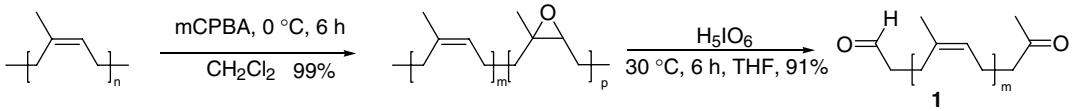
Received 22 March 2007; revised 11 July 2007; accepted 16 July 2007
Available online 21 July 2007

Abstract—The first selective reductive amination of carbonyl telechelic oligoisoprene (CTPI) using $NaBH(OAc)_3$ as the reducing agent is described. An access to tri- and tetrafunctionalized oligoisoprenes is realized in two or three steps from CTPI in high yield.

The design and the development of new polymers are a continuous task for polymerists to target specific applications. In this respect, our group has developed an interesting method[1] (Scheme 1) consisting of a selective cleavage of synthetic or natural high molecular weight polyisoprene leading to liquid carbonyl telechelic *cis*-1,4 polyisoprenes (CTPI) with controlled microstructure, and with precise chain ends and functionalities (fn = 2). These oligoisoprenes were engaged as precursors in the synthesis of linear polyurethanes,[2] which have showed very interesting physico-chemical and biological[3] properties as thermoplastic elastomers. To explore the scope of these oligomers, we were strongly involved in the reactivity control of each CTPI carbonyl chain end. Thus we particularly focused our efforts on regioselective chemical modifications using direct reductive amination. Different chemical modifications were tested affording polyfunctional oligomers. Beyond the fundamental interest of such investigations, the objectives behind chemical modification research are twofold: on one hand to prepare new materials for specific uses in nontraditional areas, on the other hand to find alternative methodologies to conventional ones using environmentally friendly sources such as natural rubber latex.

Direct reductive amination of carbonyl compounds, which allows a one step access to amine from aldehydes or ketones, is a well known reaction.[4,5] However, to our knowledge, very few authors described a selective direct reductive amination towards aldehydes over ketones.

Thus, Oshawa and co-workers[6] carried out inter- and intramolecular competition reactions in order to compare the reactivity of aldehyde and ketone groups towards aniline. They determined a complete selectivity in favour of aldehydes under Hantzsch dihydropyridines reduction[7,8] conditions, ketones remaining unchanged. Rather than using similar reductive conditions, we opted for the more traditional $NaBH(OAc)_3$ reducing agent because of its commercial availability and smooth



Scheme 1.

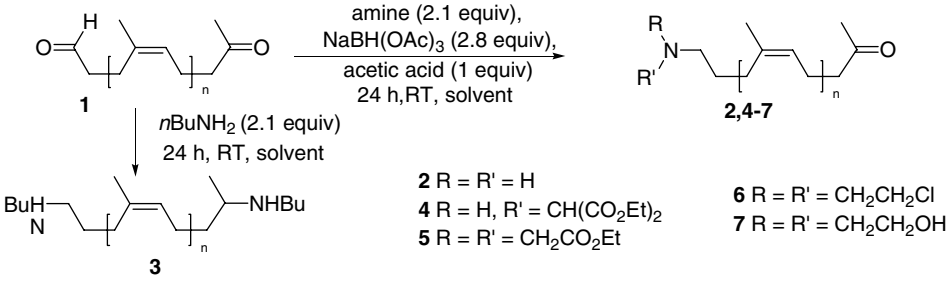
Keywords: Controlled degradation of polyisoprenes; Direct reductive amination; Polyfunctionalized oligoisoprenes.
* Corresponding author. Tel.: +33 243833540; e-mail: jean-francois.pilard@univ-lemans.fr

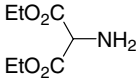
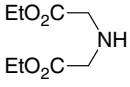
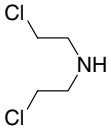
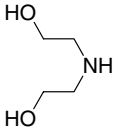
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.07.089

reactivity demonstrated not to reduce neither isoprene double bond nor ketone.[4c] The first experiments were carried out with butylamine,[1b] a very reactive primary amine. Used in excess, it has been demonstrated that the reductive amination occurred at the two chain ends (Table 1, entry 1), whereas used in default (entry 2), a mixture of oligomers was obtained. On the other hand, we have shown that the use of ammonium acetate towards CTPI (entry 3) led to a clean and selective reductive amination of the aldehyde function only after activation with acetic acid (Scheme 2). If this latter derivative showed a good stability at room temperature a fast polycondensation occurred when heated above 40 °C.[9]

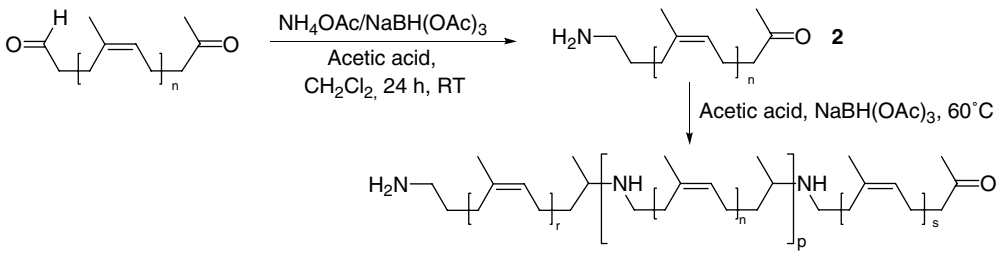
When less reactive amines are used, a complete selectivity was observed. Thus, when diethyl aminomalonate was used (entry 4), the ^{1}H NMR investigation showed the disappearance of characteristic signals (CHO and CH_2 α to the aldehyde) indicating a total conversion of the aldehydic group, whereas the ketone entity did not react even when 2 equiv of amine were used.[10] This suggested that the unshared pair of electron on the amine nitrogen was not sufficiently nucleophilic to add

Table 1. Direct reductive amination of CTPI



Entry	Amine[a]	Product	Yield (%)
1	*n*-Butylamine	**3**	86
2	*n*-Butylamine[b]	—	ND[c]
3	NH_4OAc	**2**	86
4		**4**	67
5		**5**	84
6		**6**	97
7		**7**	77

[a] For entries 1, 2, 3, 5, 7: dichloroethane was used as the solvent of the reaction; for entries 4 and 6: a mixture of dichloroethane/DMF.
[b] 1.2 equiv of amine was used.
[c] Not determined, mixture of oligomers.



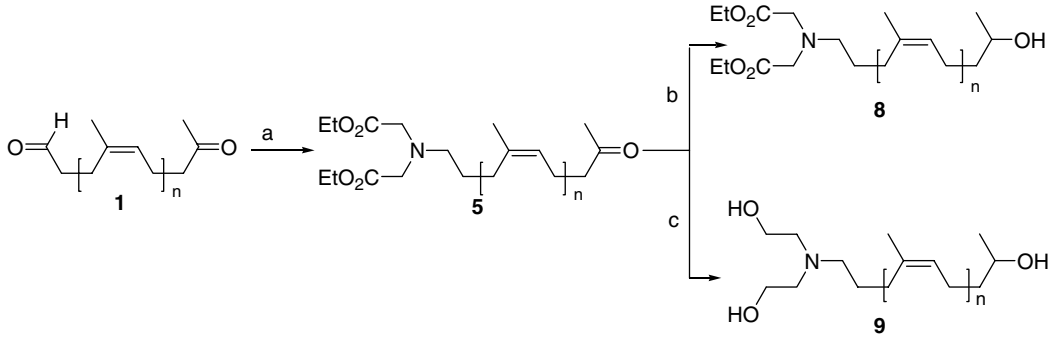
Scheme 2.

to the ketone. Moreover, no competing aldehyde[5,11] and/or ketone reduction was observed. Secondary amines were then tested (entries 5–7) and afforded amine oligomers in high yields. We confirmed that the selectivity of the reductive amination of aldehydes over ketones was dependent on the nature and the substitution pattern of the amine.

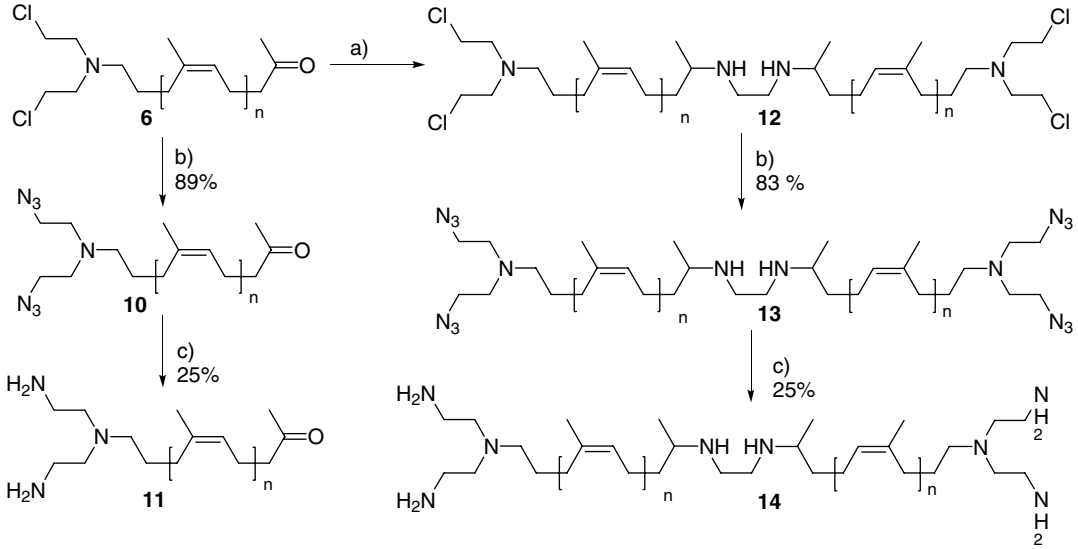
It is worth noting that alcohol oligoisoprene **8**[12] can be prepared by a selective reduction of diester **5** using $NaBH_4$ as depicted in Scheme 3. From the same diester **5**, the interesting triol **9**[13] was synthesized switching the reductant to $LiAlH_4$ (Scheme 3). At last, diol **7** was produced directly from CTPI (entry 7). Thus, three complementary oligoisoprenes bearing hydroxy groups were obtained from CTPI in one or two steps. These precursors could offer various possibilities to design new polymers. From dichlorooligoisoprene **6**, chlorines are easily substituted by azido group (Scheme 4). Organic azides[14] are particularly useful intermediates in synthetic chemistry because they are readily introduced into molecules. They can be engaged in 1,3-dipolar additions or they can be transformed into a variety of functionalities such as azo or amine compounds in order to obtain polyurethane foams and coatings. Finally, reduction of **10**[15] using Staudinger conditions[16] afforded diamino oligoisoprene **11**[17] confirmed by IR investigations showing the disappearance of azido bands.

From a telechelic oligomer, a trifunctional oligomer was obtained with a possible orthogonal modification of the various functionalities. We, then, focused on tetrafunctional oligoisoprenes. Indeed, tetraamine macromonomer **14**[18] could be obtained by a double reductive amination of end chain ketone employing *N*,*N*′-ethylene diamine and starting from **6**. In this case, ethylene diamine in the presence of acetic acid is nucleophilic enough to form iminium salt and dimer **12** was obtained in good yield. Chlorines were then substituted with azido groups, which were easily reduced in primary amine in nonoptimized yield (Scheme 4).

In summary, CTPI can be modified selectively without any protection of the ketone moiety by reductive amination using prefunctionalized amine. Chemical modifications of these functionalities lead in two or three steps to interesting tri or tetrafunctionalized oligomers. A wide panel of macromolecules with different degree of



Scheme 3. Reagents and conditions: (a) reductive amination; (b) $NaBH_4$, 60 °C, 6 h (83%); (c) $LiAlH_4$, Et_2O, rt, 5 h (68%).



Scheme 4. Reagents and conditions: (a) $NH_2CH_2CH_2NH_2$, $NaBH(OAc)_3$, CH_3CO_2H, DCE, 24 h, rt (90%); (b) NaN_3, THF/DMF, 24 h, 75 °C; (c) PPH_3, THF, H_2O.

functionality is obtained and could lead to various hyperbranched polymers.

Acknowledgement

The authors wish to acknowledge the Région des Pays de la Loire, the Réseau Materiaux Polymères Plasturgie (RMPP), the Université du Maine and CNRS for their financial support.

References and notes

1. (a) Gillier-Ritoit, S.; Reyx, D.; Campistron, I.; Laguerre, A.; Singh, R. P. *J. Appl. Polym. Sci.* **2003**, *87*, 42–46; (b) Kebir, N.; Morandi, G.; Campistron, I.; Laguerre, A.; Pilard, J.-F. *Polymer* **2005**, *46*, 6844–6854.
2. (a) Kebir, N.; Campistron, I.; Laguerre, A.; Pilard, J.-F.; Bunel, C.; Couvercelle, J.-P.; Gondard, C. *Polymer* **2005**, *46*, 6869–6877; (b) Kebir, N.; Campistron, I.; Laguerre, A.; Pilard, J.-F.; Bunel, C.; Couvercelle, J.-P. *e-Polymer* **2006**, *48*, 1–14.
3. Kebir, N.; Campistron, I.; Laguerre, A.; Pilard, J.-F.; Bunel, C.; Jouenne, T. *Biomaterials* **2007**, *28*, 4200–4208.
4. For reviews on reductive amination of carbonyl compounds see: (a) Lane, C. F. *Synthesis* **1975**, 135; (b) Hutchins, R. O.; Hutchins, M. K.; Trost, B. M. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 8, pp 25–78; (c) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Pro. Res. Dev.* **2006**, *10*, 971–1036.
5. For recent interesting reductive amination, see: (a) Menche, D.; Böhm, S.; Li, J.; Rudolph, S.; Zander, V. *Tetrahedron Lett.* **2007**, *48*, 365–369; (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86; (c) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. *Adv. Synth. Catal.* **2006**, *348*, 1289; (d) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203–211; (e) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
6. Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105–3108.
7. For a recent example of Hantzsch dihydropyridines use, see: Martin, N. A. J.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369.
8. Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *J. Org. Chem.* **1997**, *62*, 3582–3585.
9. The reaction performed at 60 °C went to completion after 4 h (disappearence of characteristic signals in ^{1}H NMR). Molecular weight, measured by light diffusion has reached 50,000 g/mol.
10. *General synthetic procedure for reductive amination of CTPI*: Carbonyl telechelic *cis*-1,4-oligoisoprene **1** (0.04 mol/L) and amine (2.1 equiv, see Table 1) in solvent (dichloroethane or dichloroethane/DMF) were mixed in a three-necked round bottom flask. The solution was then treated with sodium triacetoxyborohydride (2.8 equiv) and glacial acetic acid (1 equiv) at room temperature. After stirring for 24 h, the reaction mixture was washed with 1 N NaOH solution. The organic layer was then dried ($MgSO_4$) and concentrated to dryness. ^{1}H NMR (400 MHz, $CDCl_3$) of α-carbonyl-ω-*N*-malonateaminotelechelic *cis*-1,4-oligoisoprene **4**, δ (ppm): 1.28 (t, $J = 7.6$ Hz, CH_3 ester), 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.13 (s, CH_3 α to ketone), 2.26 (m, CH_2 β to ketone), 2.43 (t, $J = 7$ Hz, CH_2 α to ketone), 2.57 (m, CH_2 α to nitrogen), 4.03 (CH malonate), 4.28 (q, CH_2 ester), 5.12 (m, CH isoprene); IR (KBr): 3400, 1748, 1721, 1664 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) of α-carbonyl-ω-*N*,*N*-diethylacetateaminotelechelic *cis*-1,4-oligoisoprene **5**, δ (ppm): 1.28 (t, $J = 7.5$ Hz, CH_3 ester), 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.13 (s, CH_3 α to ketone), 2.26 (m, CH_2 β to ketone), 2.43 (t, $J = 7.9$ Hz, CH_2 α to ketone), 2.69 (m, CH_2 α to nitrogen), 3.54 (s, CO-CH_2–N), 4.17 (q, $J = 7.5$ Hz, CH_2 ester), 5.12 (m, CH isoprene); IR (KBr): 1748, 1721, 1664, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) of α-carbonyl-ω-*N*,*N*-dichloroethylaminotelechelic *cis*-1,4-oligoisoprene **6**, δ (ppm): 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.13 (s, CH_3 α to ketone), 2.26 (m, CH_2 β to ketone), 2.43 (t, $J = 7.3$ Hz, CH_2 α to ketone), 2.54 (m, CH_2 α to nitrogen), 2.86 (t, $J = 7.2$ Hz, Cl–CH_2–CH_2–N), 3.49 (t, $J = 7.2$ Hz, Cl–CH_2–CH_2–N), 5.12 (m, CH isoprene); IR (KBr): 1721, 1664, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) of α-carbonyl-ω-*N*,*N*-dihydroxyethylaminotelechelic *cis*-1,4-oligoisoprene **7**, δ (ppm): 1.67 (s, CH_3 isoprene), 2.04 (s,$2 \times CH_2$ isoprene), 2.13 (s, CH_3 α to ketone), 2.26 (m, CH_2 β to ketone), 2.43 (t, $J = 7.9$ Hz, CH_2 α to ketone), 2.54 (m, CH_2 α to nitrogen), 2.69 (t, $J = 5.4$ Hz, HO–CH_2–CH_2–N), 3.63 (t, $J = 5.4$ Hz, HO–CH_2–CH_2–N), 5.12 (m, CH isoprene); IR (KBr): 3400, 1721, 1664 cm^{-1}.
11. Aldehyde could be reduced before imine formation, see: Caufield, T. J.; Prasad, C. V. C.; Prouty, C. P.; Saha, A. K.; Sardano, M.; Schairer, W. C.; Yawman, A.; Upson, D. A.; Kruse, L. I. *Bioorg. Med. Chem. Lett.* **1993**, *12*, 2771.
12. Synthesis of α-hydroxy-ω-*N*,*N*-diethylacetateaminotelechelic *cis*-1,4-oligoisoprene **8**: Sodium borohydride ($NaBH_4$) (49 mg, 1.29 mmol) in 5 mL of THF was added dropwise to a solution of α-carbonyl,ω-*N*,*N*-diethylacetateaminotelechelic *cis*-1,4-oligoisoprene **5** (0.4 g, 0.21 mmol) in 10 mL of THF. After stirring for 6 h at 60°C, hydrolysis of borane complexes was performed after cooling by dropwise addition of THF solution on ice. The reaction mixture was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to afford **8** in 83 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18 (d, $J = 6.5$ Hz, CH_3 β to OH), 1.26 (t, $J = 7.3$ Hz, CH_3 ester), 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.69 (m, CH_2 α to nitrogen), 3.54 (s, CO–CH_2–N), 3.80 (m, CH–OH), 4.17 (q, $J = 7.3$ Hz, CH_2 ester), 5.12 (m, CH isoprene); IR (KBr): 3450, 1748, 1664 cm^{-1}.
13. Synthesis of α-hydroxy-ω-*N*,*N*-dihydroxyethylaminotelechelic *cis*-1,4-oligoisoprene **9**: To a solution of lithium aluminohydride 1 M in Et_2O (1.05 mL, 1.05 mmol) in a three-necked round bottom flask with magnetic stirring under nitrogen atmosphere, α-carbonyl,ω-*N*,*N*-diethylacetateaminotelechelic *cis*-1,4-oligoisoprene **5** (0.281 g, 0.15 mmol) in 15 mL of Et_2O was added at 0 °C. After stirring for 5 h at room temperature, hydrolysis of lithioaluminate complexes was performed by dropwise addition of water at 0 °C. The organic layer was separated and dried. The solvent was removed under reduced pressure to give **9** in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18 (d, $J = 6.1$ Hz, CH_3 β to OH), 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.54 (m, CH_2 α to nitrogen), 2.67 (t, $J = 5.4$ Hz, HO–CH_2–CH_2–N), 3.62 (t, $J = 5.4$ Hz, HO–CH_2–CH_2–N), 3.80 (m, CH–OH), 5.12 (m, CH isoprene); IR (KBr): 3400, 1664, 1448 cm^{-1}.
14. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
15. *Synthesis of α-carbonyl,ω-N,N-diazidoethylaminotelechelic cis-1,4-oligoisoprene* **10**: α-carbonyl,ω-*N*,*N*-dichloroethyl-

aminotelechelic *cis*-1,4-oligoisoprene **6** (1.477 g, 0.71 mmol) in 8 mL of THF and 15 mL of DMF and sodium azide (NaN_3, 0.186 g, 2.86 mmol) were stirred for 24 h at 75°C into a three necked round bottom flask under nitrogen atmosphere. The reaction mixture was poured into 5 mL of cold H_2O and the product was extracted with Et_2O. The organic layer was dried and the solvent was removed under reduced pressure to give **10** in 89% yield. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.13 (s, CH_3 α to ketone), 2.26 (m, CH_2 β to ketone), 2.43 (t, $J = 7.3$ Hz, CH_2 α to ketone), 2.51 (m, CH_2 α to nitrogen), 2.71 (t, $J = 5.8$ Hz, N_3–CH_2–CH_2–N), 3.30 (t, $J = 5.8$ Hz, N_3–CH_2–CH_2–N), 5.12 (m, CH isoprene); IR (KBr): 2120, 1721, 1664 cm^{-1}. A similar procedure was used to synthesize **13** (83%). ^1H NMR (400 MHz, $CDCl_3$) of **13**, δ (ppm): 1.05 (d, $J = 6.2$ Hz, CH_3 β to NH), 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.61 (m, CH α to NH), 2,71 (t, $J = 5.8$ Hz, N_3–CH_2–CH_2–N), 2.75 (m, NH–CH_2–CH_2–NH), 3.30 (t, $J = 5.8$ Hz, N_3–CH_2–CH_2–N), 5.12 (m, CH isoprene);. IR (KBr): 2120, 1721, 1664 cm^{-1}.

16. For a review of the Staudinger reaction, see: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437–472.
17. *Synthesis of α-carbonyl,ω-N,N-diaminoethylaminotelechelic cis-1,4-oligoisoprene* **11**: a suspension of triphenylphosphine (0.321 g, 1.45 mmol) in 2 mL of H_2O was added to α-carbonyl,ω-*N*,*N*-diazidoethylaminotelechelic *cis*-1,4-oligoisoprene **10** (1.256 g, 0.60 mmol) in 10 mL of THF into a round bottom flask. After 24 h stirring at room temperature, the reaction mixture was washed with H_2O (5 mL). The product was extracted with Et_2O and dried ($MgSO_4$). The solvent was removed under reduce pressure to give **11**. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67 (s, CH_3 isoprene), 2.04 (m, $2 \times CH_2$ isoprene), 2.13 (s, CH_3 α to ketone), 2.26 (m, CH_2 β to ketone), 2.43 (m, CH_2 α to ketone), 2.52 (m, $3 \times CH_2$ α to nitrogen), 2.74 (t, $J = 7.3$ Hz, H_2N–CH_2–CH_2–N), 5.12 (m, CH isoprene); IR (KBr): 1721, 1664, 1448 cm^{-1}. A similar procedure was used to synthesize **14** (25%). ^1H NMR (400 MHz, $CDCl_3$) of **14**, δ (ppm): 1.03 (d, $J = 6.2$ Hz, CH_3, β to NH), 1.67 (s, CH_3 isoprene), 2.04 (m, $2 \times CH_2$ isoprene), 2.48 (t, $J = 7.3$ Hz, NH_2–CH_2–CH_2–N), 2.51 (m, CH_2–N), 2.64 (m, CH α to NH), 2.71 (t, $J = 7.3$ Hz, NH_2–CH_2–CH_2–N), 2.74 (m, NH–CH_2–CH_2–NH); IR (KBr): 1664, 1448 cm^{-1}.
18. *Preparation of N,N-dichloroethylaminotelechelic macromonomer* **12**: α-carbonyl,ω-*N*,*N*-dichloroethylaminotelechelic *cis*-1,4-oligoisoprene **6** (0.992 g, 0.45 mmol) in 10 mL of dichloroethane and ethylene diamine (15 μL, 0.23 mmol) were mixed into a three-necked round bottom flask with magnetic stirring under nitrogen atmosphere. The mixture was then treated with glacial acetic acid (26 μL, 0.45 mmol) and sodium triacetoxyborohydride (0.137 g, 0.62 mmol). After stirring for 24 h at room temperature under nitrogen atmosphere, the reaction mixture was washed with 1 N NaOH solution and the product was extracted with dichloromethane. The organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to give **12** in 90% yield. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.06 (d, $J = 6.5$ Hz, CH_3 β to NH), 1.67 (s, CH_3 isoprene), 2.04 (s, $2 \times CH_2$ isoprene), 2.54 (m, CH_2 α to N), 2.62 (m, CH α to NH), 2.77 (m, NH–CH_2–CH_2–N–), 2.86 (t, $J = 6.8$ Hz, Cl–CH_2–CH_2–N), 3.49 (t, $J = 6.8$ Hz, Cl–CH_2–CH_2–N), 5.12 (m, CH isoprene); IR (KBr): 1664 cm^{-1}.