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COMMUNICATION

Nitrone-mediated radical coupling reactions: a new synthetic tool exemplified on dendrimer synthesis†

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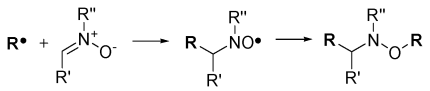
A synthetic strategy employing nitrones as radical spin traps is presented on the example of the efficient generation of novel dendrimers *via* a combination of radical and classical *'click'* chemistry.

Nitrones constitute an efficient class of compound capable of acting as both 1,3-dipoles in cycloaddition reactions[1–3] or in radical reactions as spin trap agents.[4] It is through cycloaddition reactions that nitrones have found synthetic application. It comes, however, as a surprise that their ability to selectively trap radicals is largely under-utilized in chemical syntheses even though nitrones can potentially be applied as a synthetic device in radical chemistry. Upon addition of radicals, nitrones form nitroxides in high yields, which can subsequently react with a second radical species forming an alkoxyamine (see Scheme 1). In such a radical coupling reaction, a multi-functional compound is derived with two potential functional units stemming from the radical species situated at both ends as well as a precisely centered-alkoxyamine group which may carry a secondary functionality (*e.g.* alkynyl, hydroxyl, aldehyde, *etc.*) in a mid-chain position. Thus, the radical spin capturing reaction may provide an attractive avenue for the synthesis and fast assembly of complex molecular architectures.



Scheme 1 Spin trapping reaction between radicals R• and a nitrone to form an alkoxyamine.

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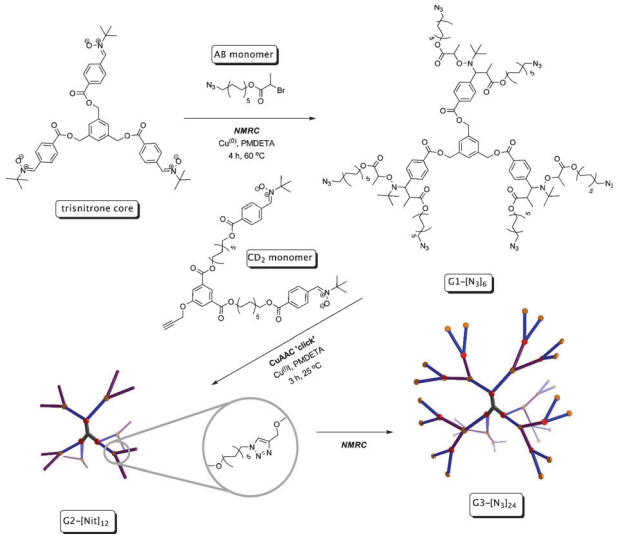
We have earlier demonstrated that this nitrone-mediated radical coupling (NMRC)[5–7] works very efficiently with macromolecules. In here, we wish to demonstrate that the same reaction also allows for excellent proficiency in non-polymer reactions. To highlight the efficiency, we have chosen to use the NMRC reaction for the build-up of a dendrimer.

For the dendrimer synthesis, a combination of radical (NMRC) and '*click*'[8] chemistries (copper catalyzed azide alkyne cycloaddition, CuAAC) was employed in a divergent growth approach. Since nitrones are able to react with two radical species resulting in the doubling of functional groups with the newly generated alkoxyamine situated in a mid-position, branch points are readily created. This allows for the generation of higher order structures and thus such a dendrimer synthesis approach is an ideal example representing the innovation of nitrone radical chemistry. In addition, the extremely well-defined structure of dendrimers is associated with unique physical properties. Thus, these entities have found many useful applications especially in the biomedical field,[9–11] yet generating such materials is synthetically often challenging. The NMRC reaction will therefore add to and complement the current efficient synthesis methodologies.[12]

As mentioned above, the NMRC reaction is built on our experience with the recently developed enhanced spin capturing polymerization (ESCP),[6,7,13–15] which was inspired by earlier studies employing nitrones by our colleagues.[16] The dendrimer synthesis is based on three starting compounds as given in Scheme 2: (i) a trisnitrone core; (ii) an AB monomer that bears an azide functionality at one end and a 2-bromopropionate group at the other (which when activated by a copper/ligand catalyst system generates acrylate-typed radicals that are to be captured by the nitrone) and (iii) a CD_2 monomer carrying one alkyne moiety and two nitrone functions. Both AB and CD_2 monomers are designed to have sufficiently long alkyl chain spacers (11 CH_2 groups) between the functional groups to ensure there is enough flexibility while minimizing steric hindrance during the radical coupling reactions.

As indicated in Scheme 2, the first generation dendrimer, G1-$[N_3]_6$, was synthesized by reacting the trisnitrone core with an excess of AB monomer (5 eq. per nitrone) under typical NMRC reaction conditions, *i.e.* in the presence of 1 eq. of copper powder and the ligand PMDETA for 4 h at 60 °C. The integrity of the azide functionality remains intact under these



Scheme 2 Overall employed strategy in the synthesis of up to third generation dendrimers *via* repetitive NMRC and '*click*' reactions.

conditions. After the removal of the copper complex, the product was further purified by column chromatography and subsequently used directly in the next step without the need for any protection/deprotection reaction step. The second generation, G2-$[Nit]_{12}$, was obtained *via* CuAAC of the azide groups of G1-$[N_3]_6$ with the alkyne of the CD_2 monomer (1.1 eq. of alkyne per azide). It is worth mentioning that although the nitrones may potentially undergo cycloaddition reactions too with the alkynes, this side product was not detected in the product mixture and it may thus be assumed that the azides react faster and therefore preferentially with the alkynes compared to nitrone–alkyne cycloaddition reactions in this particular system. The copper catalyst is removed by simply percolating the G2-$[Nit]_{12}$ over a column of basic alumina. No further purifications were necessary apart from excess monomer removal *via* dialysis in ethanol/chloroform.

In the next step, each of the twelve nitrone groups on the periphery of G2-$[Nit]_{12}$ was further functionalized to yield G3-$[N_3]_{24}$ *via* NMRC with only slightly increased amounts of AB monomer (8 eq.) to ensure maximum functionalization. An excess of monomer was only employed to ensure high reaction rates, the same reactions could also be carried out with less equivalents of the AB monomer provided the NMRC reaction was optimized by—for instance—using a less activated copper/ligand system.[5] As will be shown in the following, the obtained third generation dendrimer is of high purity and no indication for a loss of functionality is given. Thus, although we did not attempt to proceed to higher generations in the framework of this study, no reason is seen why the reaction could not be driven to higher generations. However, it must be noted that the kinetics of the current NMRC reactions were not optimized as stated above and thus lower than optimum yields may be obtained when the formed dendrimers are to be extrapolated to higher generation structures. Nevertheless, the overall approach required minimal column purification. In addition, each functionalization step resulted directly in the increase in dendrimer generations, thus placing the approach among other highly efficient dendrimer

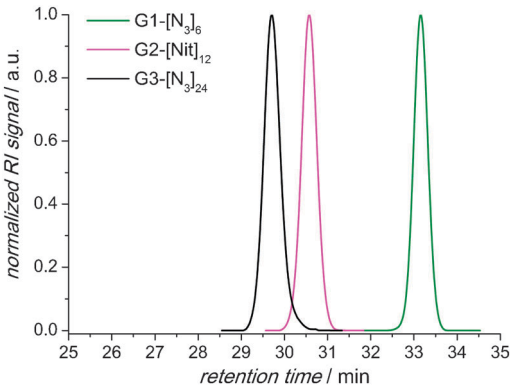


Fig. 1 SEC traces of the formed dendrimers.

synthesis strategies such as the ones that are based on thiol-yne[12a,17] and thiol-ene[12b,c] reactions. The present NMRC approach is best comparable to thiol-yne methodologies since both methods allow for addition of two moieties *via* a radical process. Thiol-yne is known to be also efficient and fast. It should, however, be noted that the synthesis of functional nitrones is relatively simple and thus easily applicable.

The successful formation of the dendrimers *via* the described approach was followed *via* size exclusion chromatography (SEC) (see Fig. 1). With each generation, a clear shift towards higher molecular weights (correlated by the decrease in retention times) is observed. The distributions are, as indicated by the measured *PDI* (see Table 1), practically monodisperse indicating that all functionalities are converted in each reaction step. Table 1 also lists the theoretical average molecular weights, M_n, of each dendrimer structure as well as those determined by SEC, ^{1}H-NMR and mass spectrometry (MS) analysis. The values measured by SEC are—not surprisingly—inaccurate given that their values are based on a polystyrene calibration. Therefore, they do not reflect the actual molecular weights. Nonetheless, SEC remains an excellent technique in providing consistent qualitative analysis. The values determined by ^{1}H-NMR and MS on the other hand are more accurate and thus in close agreement with the theoretical values. For the MS data of G2 it should be noted that the mass was calculated on the basis of multiple charged species, hence the obtained value is closer to the isotope-averaged mass rather than the monoisotopic value, therefore explaining the relatively large deviation between the experiment and theoretical value.

Fig. 2 shows the ^{1}H-NMR spectra of the end group regions of the synthesized dendrimers. An important point to note based on the NMR spectra is that the formation of diastereomers caused by the alkoxyamines may give the false impression that the products are impure. The overlap of

Table 1 Theoretical and experimental average molecular weights (in g mol^{-1}) of the dendrimers shown in Scheme 2. SEC relative to a poly(styrene) calibration

Dendrimer	Theoretical	^{1}H NMR	MS	SEC[a]
G1-$[N_3]_6$	2386.58	2487	2387.1	3600 (1.006)
G2-$[Nit]_{12}$	8185.94	8874	8189.5	11 600 (1.007)
G3-$[N_3]_{24}$	14 632.57	16 827	—	17 400 (1.011)

[a] The values in brackets are polydispersity indices, *PDI*.

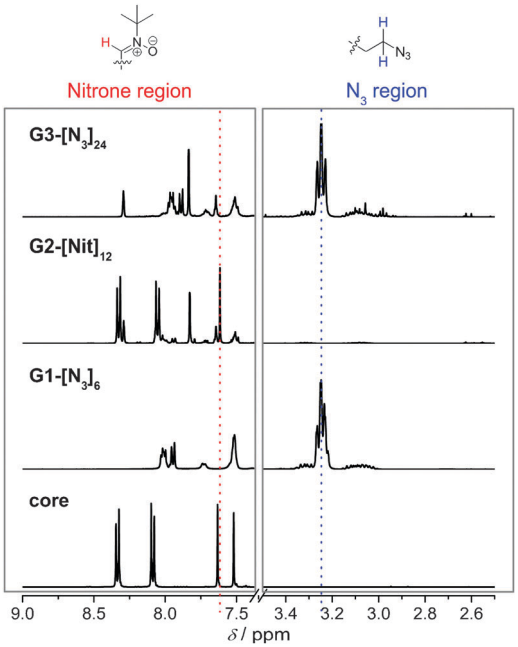


Fig. 2 ^{1}H-NMR spectra of the end group regions evidencing the chemical transformations as the dendrimers increase in generations. The dotted lines indicate where the protons in the α-position of the azide group and the nitrone protons lie in their respective regions. The full NMR spectra can be found in the ESI.†

different aromatic protons may also mislead the reader to think likewise. In spite of this, the products are in fact pure and the chemical transformations of the dendrimers as they progressively increase in generations were successfully monitored by the disappearance/reappearance of the key protons associated with the functional groups. In the synthesis of G1-[N_3]$_6$, the nitrone proton at 7.63 ppm originating from the trisnitrone core clearly disappeared and a new peak (3.20–3.28 ppm) corresponding to the protons on the α position of the azide groups occurred. The nitrone protons reappeared as the azide end groups undergo CuAAC reactions to yield G2-[Nit]$_{12}$. Along with this nitrone-characteristic proton, a new peak belonging to the proton of the triazole ring was formed at 7.65 ppm. When subjecting the second generation dendrimer to NMRC reactions, the nitrone protons disappear again while the α-protons of the azides reoccur, thus confirming the formation of G3-[N_3]$_{24}$.

NMRC is for the first time introduced as a facile synthetic reaction for the preparation of multifunctional alkoxyamines from nitrones and a suitable radical source. The efficiency of this synthetic strategy is demonstrated on the formation of dendrimers based on an AB/CD_2 monomer approach employing both the nitrone-mediated radical coupling reaction as well as CuAAC '*click*' chemistry. Both SEC and ^{1}H-NMR confirm the successful synthesis of the targeted dendritic structures. The synthesis method only requires a minimum number of purification procedures and no protection/deprotection steps, thus demonstrating the viability of nitrone radical chemistry in organic synthesis.

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Notes and references

1 (*a*) J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473–495; (*b*) K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 863–909.
2 L. Vretik and H. Ritter, *Macromolecules*, 2003, **36**, 6340–6345.
3 M. Heinenberg and H. Ritter, *Macromol. Chem. Phys.*, 1999, **200**, 1792–1805.
4 E. G. Janzen, *Acc. Chem. Res.*, 1971, **4**, 31–40.
5 E. H. H. Wong, C. Boyer, M. H. Stenzel, C. Barner-Kowollik and T. Junkers, *Chem. Commun.*, 2010, **46**, 1959–1961.
6 E. H. H. Wong, M. H. Stenzel, T. Junkers and C. Barner-Kowollik, *Macromolecules*, 2010, **43**, 3785–3793.
7 E. H. H. Wong, T. Junkers and C. Barner-Kowollik, *Polym. Chem.*, 2011, **2**, DOI: 10.1039/C0PY00377H.
8 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (*b*) C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad and W. Van Camp, *Angew. Chem., Int. Ed.*, 2011, **50**, 60–62.
9 W.-D. Jang, K. M. K. Selim, C.-H. Lee and I.-K. Kang, *Prog. Polym. Sci.*, 2009, **34**, 1–23.
10 D. Astruc, E. Boisselier and C. Ornelas, *Chem. Rev.*, 2010, **110**, 1857–1959.
11 P. Posocco, S. Pricl, S. Jones, A. Barnard and D. K. Smith, *Chem. Sci.*, 2010, **1**, 393–404.
12 (*a*) G. Chen, J. Kumar, A. Gregory and M. H. Stenzel, *Chem. Commun.*, 2009, 6291–6293; (*b*) K. L. Killops, L. M. Campos and C. J. Hawker, *J. Am. Chem. Soc.*, 2008, **130**, 5062–5064; (*c*) P. Antoni, M. J. Robb, L. Campos, M. Montanez, A. Hult, E. Malmstrom, M. Malkoch and C. J. Hawker, *Macromolecules*, 2010, **43**, 6625–6631; (*d*) P. Antoni, D. Nystroem, C. J. Hawker, A. Hult and M. Malkoch, *Chem. Commun.*, 2007, 2249–2251.
13 E. H. H. Wong, T. Junkers and C. Barner-Kowollik, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 7273–7279.
14 E. H. H. Wong, M. H. Stenzel, T. Junkers and C. Barner-Kowollik, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 1098–1107.
15 T. Junkers, E. H. H. Wong, M. H. Stenzel and C. Barner-Kowollik, *Macromolecules*, 2009, **42**, 5027–5035.
16 (*a*) D. Benoit, V. Chaplinski, R. Braslau and C. J. Hawker, *J. Am. Chem. Soc.*, 1999, **121**, 3904–3920; (*b*) M.-O. Zink, A. Kramer and P. Nesvadba, *Macromolecules*, 2000, **33**, 8106–8108; (*c*) R. B. Grubbs, J. K. Wegrzyn and Q. Xia, *Chem. Commun.*, 2005, 80–82; (*d*) V. Sciannamea, R. Jerome and C. Detrembleur, *Chem. Rev.*, 2008, **108**, 1104–1126.
17 R. Hoogenboom, *Angew. Chem., Int. Ed.*, 2010, **49**, 3415–3417.