FACULTY OF SCIENCES

One-pot synthesis routes towards sustainable urazoles and their potential in polymer applications

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Supervisors: Prof. Dr. Filip Du Prez
Guide: Laetitia Vlaminck

Academic Year 2016–2017

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Science in Chemistry

GHENT UNIVERSITY

FACULTEIT WETENSCHAPPEN

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One-Pot Synthesis Routes Towards Sustainable Urazoles and their Potential in Polymer Applications

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Abstract: In this work, two sustainable synthesis routes towards urazoles were elaborated, which were based on amines as starting compounds instead of toxic isocyanates. Furthermore, solvents were avoided as much as possible and equimolar amounts were used. High yields were obtained with the two routes, however, they are complementary as the first route is more interesting for non-functional urazoles, while the second route can also be applied to obtain functional urazoles. With the optimized synthesis of sustainable urazoles, their application in linear and hyperbranched polymers was tested.

Keywords: green chemistry, isocyanate-free, urazole, one-pot, hyperbranched polymers

Introduction

Plastics have become an essential part of our everyday life, as can be seen in the production volumes, which have surged over the past 50 years. This increase can be attributed to the broad application window of plastics, especially in packaging.[1] Because of the increasing interest in plastics, two large consequences emerged, namely the depleting stock of fossil resources[2] and the growing plastic waste stream, both on land and in the ocean.[3] Furthermore, oil prices are expected to increase, and actions need to be taken to avoid the use of materials based on fossil resources.[4] That is why renewable resources gain more attention in the chemical industry to obtain more sustainable materials. In polymer chemistry, the awareness to achieve more sustainable plastics is growing, leading to polymers who are derived from renewable resources or can undergo biodegradation. In order to speed up this transition towards bioplastics, new research is required, in which existing processes should be redesigned and optimized again.

One of those processes which has to be redesigned is the synthesis towards urazoles. Upon oxidation of these urazoles, 1,2,4-triazolinediones or TADs are generated. They are the most reactive dienophiles and enophiles currently known.[5] A recent publication in Nature chemistry from our research group, concerning TAD chemistry, has triggered the interest of different research groups worldwide, leading to its revival in polymer chemistry.[6] For example, in the field of green chemistry, a fast crosslinking was reported between plant oils and bivalent TAD molecules.[7] Furthermore, Tang and co-workers introduced a method to enhance the mechanical strength of plant-oil based thermoplastic elastomers via TAD chemistry.[8] Another application was introduced by Vlaminck *et al.*, who proposed a post-polymerization functionalization method for acyclic diene metathesis (ADMET) derived polymers by using TAD.[9] Furthermore, sustainable applications in shape memory materials

can be found.[10] Therefore, it is interesting to synthesize urazoles in a more sustainable way because nowadays, their synthesis starts from the corresponding isocyanate, as described by Cookson in 1971.[11] The isocyanate combines with ethylcarbazate (EC) to form the corresponding semicarbazide, which undergoes cyclization under basic conditions to obtain the corresponding urazole. Not only are isocyanates limited in structural diversity, they are also very toxic.[12]

To avoid the use of these hazardous compounds and obtain a more sustainable synthesis route, carboxylic acids were proposed by Shimada *et al.* in 1990, in which case the corresponding isocyanate is formed in situ via a Curtius rearrangement with the aid of diphenylphosphoryl azide (DPPA).[13] The main disadvantage of this reaction pathway is the toxicity and price of DPPA. Therefore, another effort to improve the sustainability of urazole compounds proposed the use of amines as starting materials.[14] However, the two reaction pathways suggested by Mallakpour[15] and Breton[16] in 2007 and 2014, respectively, make use of toxic and corrosive chloroformates as one of the starting compounds. Furthermore, the amine is added in excess during the semicarbazide synthesis, inducing an extra purification step before the cyclization can be performed. This still limits the sustainability of urazole synthesis and therefore, the aim of this work was in a first step, to improve the sustainability of the amine-based urazole synthesis.

Two different pathways are proposed which are fully optimized in terms of sustainability and efficiency. The first method is based on the synthesis of an activated carbamate which further reacts with EC towards a semicarbazide. After a thermal cyclization, the urazole is obtained. In the second method, the urazole is obtained via reaction between a reactive intermediate and the amine, followed by basic or thermal cyclization. These routes are one-pot, isocyanate- and chloroformate-free procedures that make use of equimolar amounts. Furthermore, solvents and purification steps are avoided as much as possible.

The unique reactivity of TAD compounds makes them extremely useful in the field of green chemistry. After their sustainable synthesis, the TAD compounds were tested in polymer applications. Self-condensation of TAD-ene monomers towards linear and (hyper)branched polymers is investigated. As sustainability is a focus point of this work, renewable starting materials are used whenever possible. Furthermore, the reactions are performed, where possible, via fast, one-pot reaction mechanisms.

Experimental

Materials

Allylamine (Sigma-Aldrich, ≥99%), 3-amino-1-propanol (Sigma-Aldrich, 99%), aniline (Sigma-Aldrich, 99%), benzylamine (Sigma-Aldrich, 99%), bromine (Sigma-Aldrich, ≥99%), butylamine (Acros organics, ≥99%), chloroform (Sigma-Aldrich, ≥99.8%), β-citronellol (Sigma-Aldrich, 95%), cyclohexanemethylamine (TCI, ≥98%), cysteamine (Sigma-Aldrich, 95%), 1,4-diazabicyclo(2.2.2)octane (Sigma-Aldrich, ≥99%), dichloromethane (Sigma-Aldrich, ≥99.8%), diethylazodicarboxylate (TCI, 40 wt% in toluene), dimethylsulfoxide deuterated (DMSO-d_6) (Eurisotop, 99.8%), diphenylcarbonate (Acros organics, 99%), ethyl acetate (Sigma-Aldrich, 99.7%), ethyl carbazate (Sigma-Aldrich, 97%), ethylenediamine (Acros organics, ≥99%), geraniol (Alfa Aesar, 97%), n-hexane (Sigma-Aldrich, ≥97%), hydrazine monohydrate (VWR, ≥98), hydrochloric acid (Chem-Lab, 36%), magnesium sulfate (Boom), methanol (Sigma-Aldrich, 99,9%), octylamine (Sigma-Aldrich, 99%),

oleylamine (Sigma-Aldrich, ≥98%), phthalimide (TCI, ≥98%), potassium carbonate (Roth, ≥99%), tetrahydrofurfuryl amine (TCI, ≥98%), triphenylphosphine (Acros organics, 99%) were used as received.

Instrumentation

NMR spectra were recorded with a Bruker AVANCE 300 (300MHz) and a 400MHz AVANCE II Ultrashield Bruker. LC-MS analyses were performed on an Agilent Technologies 1100 series LC/MSD system with a diode array detector (DAD) and single quad MS. Differential scanning calorimetry (DSC) analyses were performed with a Mettler Toledo instrument 1/700 under nitrogen atmosphere at a heating rate of 10 °C/min. The glass transition temperatures were determined from midpoints in the second heating scan using the STARe software of Mettler-Toledo. Measurements were performed in a range of -70 to 190 °C with a rate of 10 °C/min. Thermogravimetric analyses (TGA) were performed on a Mettler Toledo TGA/SDTA 851e under nitrogen atmosphere. The sample was heated from 25 to 800 °C with a rate of 10 °C/min. The thermograms were analyzed using the STARe software from Mettler-Toledo.

Synthesis of urazoles via an activated carbamate

DPC (1 eq) was heated to 80 °C under inert atmosphere N_2, in a metal bath. After melting, a primary amine (1 eq) was added and the reaction mixture stirred for 10 minutes. EC (1 eq) was added to the reaction mixture and stirred for 2.5 h at 140 °C. The reaction mixture was further heated for 1 h at 250 °C under a gentle nitrogen flow.

Synthesis of ethyl phenyl hydrazine-1,2-dicarboxylate (EPHD)

20 g DPC (1 eq, 0.093 mol) was melted in a 250 mL flask. 20 g EC (2 eq, 0.192 mol) was added and the mixture stirred under inert atmosphere for 1 h at 80 °C. Afterwards, the product was precipitated in water and dried in a vacuum oven at 40 °C and the pure white powder was obtained. (76 %)
Chemical formula: $C_{10}H_{12}N_2O_4$. **Molecular weight:** 224.22 g/mol. **^{1}H-NMR (300 MHz, DMSO-d_6):** δ(ppm) = 1.17 (t, 3H, O-CH_2-C*H*$_3$), 4.08 (q, 2H, O-C*H*$_2$-CH_3), 7.01-7.47 (m, 5H, Ar-*H*), 9.25 (s, 1H, N*H*-CO-O-Et), 9.67 (s, 1H, Ar-O-CO-N*H*).

Synthesis of urazoles via an activated intermediate

EPHD (1 eq) was melted at 80 °C under inert atmosphere. A primary amine (1 eq) was added and the mixture was stirred for 10 minutes. Subsequently, the temperature of the reaction mixture was increased to 250 °C for 1 h and a gentle nitrogen flow was applied. The pure product was obtained. In case of functional amines (eg. 3-amino-1-propanol) and bis-amines, a basic cyclization was applied. In that case, after stirring for 10 minutes, ethanol and K_2CO_3 (5 eq) were added and the mixture was refluxed overnight. Subsequently, the reaction mixture was cooled to room temperature and acidified to pH 1 with HCl in propanol (5-6 N). The precipitate was filtered off and the reaction mixture was concentrated *in vacuo* to obtain the pure product.

Synthesis tetrameric 1,4-diazabicyclo[2.2.2]octane bromide complex (DABCO-Br)[17]

In a flask of 250 mL, 6.73 g 1,4-diazabicyclo[2.2.2]octane (1 eq, 60 mmol) was added to 100 mL chloroform. A mixture of 20 g bromine (2.1 eq, 0.125 mol) in 100 mL chloroform was added drop wise to the flask with an addition funnel and stirred for 1 h under inert atmosphere. The yellow precipitate was filtered and washed with 50 mL chloroform. Finally, the product was placed in the vacuum oven overnight at 40 °C. (99%) **Chemical formula:** $C_{24}H_{54}Br_{14}N_8$. **Molecular weight:** 1573.4 g/mol.

Synthesis of citronellyl amine or geranyl amine[18]

A mixture of phthalimide (1 eq), triphenylphosphine (1 eq), and the appropriate alcohol (1 eq) in dry THF was cooled to 0 °C. To this, diethyl azodicarboxylate (DEAD) (1 eq) in dry THF was added over a time range of 30 minutes. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue suspended in Et_2O. The precipitate was filtered and the filtrate was concentrated *in vacuo*. The product was purified using column chromatography (eluens: EtOAc). Pure product was obtained.
A mixture of N-substituted phthalimide (1 eq) and hydrazine monohydrate (1.5 eq) in methanol was heated at reflux for 1 h and then concentrated *in vacuo*. The residue was dissolved in 1 M HCl and insoluble compounds were removed by filtration. The filtrate was made basic with 5 M NaOH and extracted with Et_2O (3 x). The combined ether layer was washed with saturated brine (2 x) and dried over $MgSO_4$. Evaporation of the solvent afforded the primary amine as a yellow liquid.
Citronellyl amine: **Yield:** 69 %. **Chemical formula:** $C_{10}H_{21}N$. **Molecular weight:** 155.3 g/mol. **^{1}H-NMR (400 MHz, DMSO-d_6):** δ(ppm) = 0.84 (d, 3H, CH-CH_3), 1.04-1.52 (m, 7 H, CH_2-CH-CH_2-CH_2-NH_2), 1.57 (s, 3H, C-CH_3), 1.64 (s, 3H, C-CH_3), 1.94 (quint, 2H, CH_2-CH=C), 2.55 (m, 2H, CH_2-NH_2), 5.09 (t, 1H, CH=C).
Geranyl amine: **Yield:** 68 %. **Chemical formula:** $C_{10}H_{19}N$. **Molecular weight:** 153.27 g/mol. **^{1}H-NMR (400 MHz, DMSO-d_6):** δ(ppm) = 1.57 (s, 6H, CH_3-C-CH_3), 1.65 (d, 3H, CH_2-C-CH_3), 1.99 (m, 4H, CH_2-CH_2), 3.1 (d, 2H, CH_2-NH_2), 5.09 (t, 1H, CH-CH_2-CH_2), 5.19 (t, 1H, CH-CH_2-NH_2).

Results and discussion

Synthesis of sustainable urazoles

Two reaction routes were developed, which make use of diphenyl carbonate (DPC). DPC can be synthesized via a transesterification reaction of dimethyl carbonate (DMC) and phenol. Another, more sustainable, methodology is the direct oxidative carbonylation of phenol. These routes are highly promising because recycled phenol could be incorporated.

Route A - Via an activated carbamate

The first methodology is the more sustainable alternative of the method developed by Mallakpour in 2007. In the first step, a carbamate was formed via an addition-elimination

reaction between a primary amine and DPC at 80 °C in bulk for 10 minutes (Figure 1). ^{1}H-NMR analysis showed that the reaction was instantaneous and high-yielding, however also a minor side product was observed, even when an equimolar ratio of amine and DPC was applied. Both NMR and LC-MS proved that a urea side product (5-10 %) was formed because of double amine addition to the DPC (Figure 2). A systematic study showed that a twofold excess of amine only resulted in the urea product, while no urea was formed upon addition of two equivalents of DPC. It thus seems interesting to apply an excess of DPC. However, intermediate purification would then be necessary to remove this excess, while the urea side product is automatically removed in the thermal cyclization step afterwards. Small amounts of urea were thus not cumbersome and only affected the yield. To maintain the one-pot process, equimolar conditions were further used.

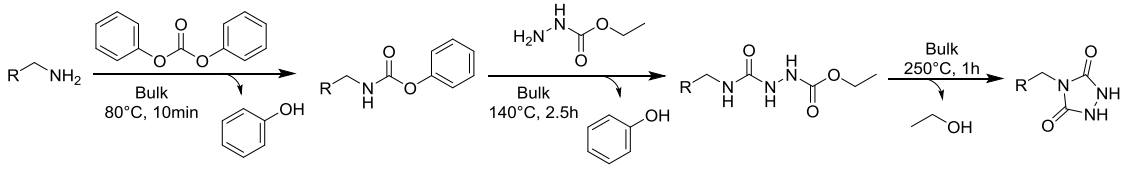

Figure 1: The urazole is obtained in a one-pot reaction via the formation of an activated carbamate, which further reacts towards the corresponding semicarbazide and finally the product is obtained via a thermal cyclization.

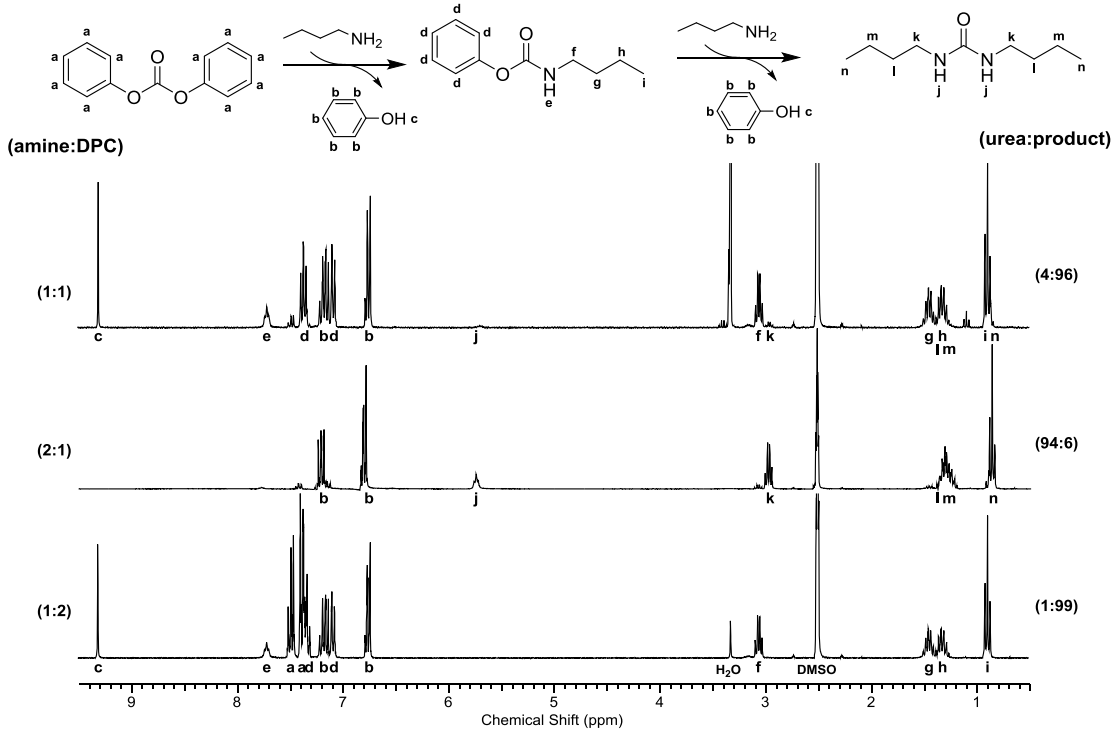

Figure 2: A systematic NMR study showed that the urea side product is the main product when an excess of amine is used, while only the carbamate is formed upon addition of 2 equivalents of DPC.

The second step of the one-pot reaction included the addition of one equivalent of EC and an increase in temperature to 140 °C, which resulted in the formation of the corresponding semicarbazide and one equivalent of phenol (Figure 1). The kinetics of this reaction were tested, by taking an NMR-sample every 30 minutes. The conversion was calculated by comparing the NH-proton of the carbamate at 7.7 ppm with the NH-proton of the

semicarbazide at 7.6 ppm. In the first 90 minutes, a linear increase was observed towards a conversion of 62 % and after 150 minutes, the reaction slowed down around a conversion of 80 % (Figure 3). As the third step included an increase in temperature and thus a further increase in reaction rate, the reaction time of the second step was kept at 2h30. While lower temperatures, for example 120 °C, also resulted in product formation, this increased the reaction time significantly. To minimize energy consumption, a temperature of 140 °C was maintained for 2h30. The urea side product that was formed in the first reaction step was unreactive towards the EC and remained unchanged in the reaction mixture.

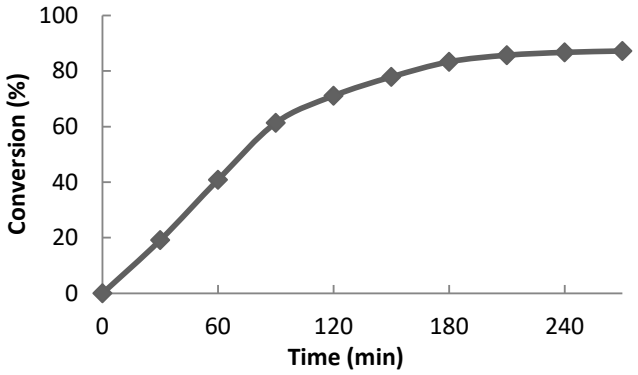

Figure 3: Kinetic analysis of the formation of benzyl semicarbazide in the second step.

The third and final step of this one-pot procedure included the cyclization of the semicarbazide to obtain the corresponding urazole (Figure 1). Paquette *et al*. proposed a thermal cyclization at 250 °C for 30 minutes, which resulted in good yields.[19] In this case, reaction was also performed at 250 °C and a gentle nitrogen flow was applied to remove the formed ethanol and the phenol that was produced in the first two reaction steps, which has a boiling point of 182 °C. The cyclization was also tested at lower temperatures, in a range of 200 °C to 240 °C. It was shown that the cyclization was also initiated at 220 °C, but in this case, 250 °C was maintained to be sure that all the phenol was removed and the reaction was completely finished. In industrial processes, the phenol could easily be recuperated and regenerated towards DPC, which can significantly increase the sustainability of the process. Again, the kinetics were tested by taking an NMR sample after every 30 minutes, but already after 30 minutes, the semicarbazide was completely converted into the corresponding urazole. Besides, the urea side product was completely removed from the reaction mixture. To make sure all phenol is removed from the reaction mixture, the reaction was kept at 250 °C for 1 h.

As can be seen in Table I, this methodology was applied to a wide range of amines with different R-groups. Aliphatic, aromatic and bifunctional amines were tested. High yields were obtained when no competitive functionalities were present, for example when butyl-, benzyl- and cyclohexanemethylamine, with yields of 86 %, 87 % and 86 % respectively. The ether-function in tetrahydrofurfurylamine proved to be resistant towards the harsh conditions of the last reaction step, as were also the mono- and disubstituted double bonds in allylamine and oleylamine. It should however be noted that in these cases a sufficient nitrogen flush is needed, to avoid side reactions with oxygen. Furthermore, it was observed that the yield was

also determined by the volatility of the investigated amine. For example, the urazole derived from allylamine had a yield of 89 %, while the heavier oleylamine had a higher yield of 96 %. It should also be noted that this methodology experienced difficulties when amines with more reactive groups were applied like an alcohol or a second amine functionality.

Because aniline has a lower nucleophilicity compared to the other amines, the carbamate could not be formed during the first step. Harada *et al*. obtained the activated carbamate with the use of isobutyric acid as catalyst and 1.2 equivalents of aniline.[20] After an extraction to remove the catalyst, the reaction mixture contained both the carbamate and the excess of aniline. Column chromatography might offer a solution to remove the excess of aniline. However, as avoidance of solvent was a main goal of this project and phenyl-urazole is one of the only commercially available urazoles, this synthesis was not continued.

In the case of 3-amino-1-propanol, it was expected that the carbamate would be the major formed product because the amine is a better nucleophile than the alcohol. But in this case, the reaction with the amine and with the alcohol towards the carbonate were both so fast that a mixture of carbamates and carbonates was obtained. The reaction mixture thus contained a lot of side products and purification was too complicated. The reaction was stopped after the first step because a sustainable synthesis with 3-amino-1-propanol was not possible via this methodology.

To obtain a bis-urazole, two equivalents of DPC were added to one equivalent of ethylenediamine. In this case, again a lot of side products were formed because both amine functionalities of ethylenediamine are equally reactive towards the bifunctional DPC and a large local excess of amines can be present in de reaction mixture. With all those side products in the reaction mixture, purification would be very difficult to obtain only the desired product.

Table I: Overview of the used amines to form the corresponding urazole and their yields. [a]: thermal cyclization, [b]: basic cyclization, n.s.: not successful. n.p.: not performed.

Amine	**Route A**	**Route B**
Butylamine	86%	89% [a]
Octylamine	96%	95% [a]
Benzylamine	87%	85% [a]
Tetrahydrofurfurylamine	87%	90% [b]
Oleylamine	96%	95% [a]
Allylamine	89%	84% [a]
Cyclohexaanmethylamine	93%	95% [a]
3-Amino-1-propanol	n.s.	78% [b]
Ethylene diamine	n.s.	92% [a]
Aniline	n.s.	n.s.

Route B - Via an activated intermediate

As the first synthesis route via the activated carbamate showed some problems when functional amines were used, a second synthesis route was investigated. This route enhances the synthesis as described by Breton *et al*., who used an activated intermediate to obtain the semicarbazide in one step (Figure 4).

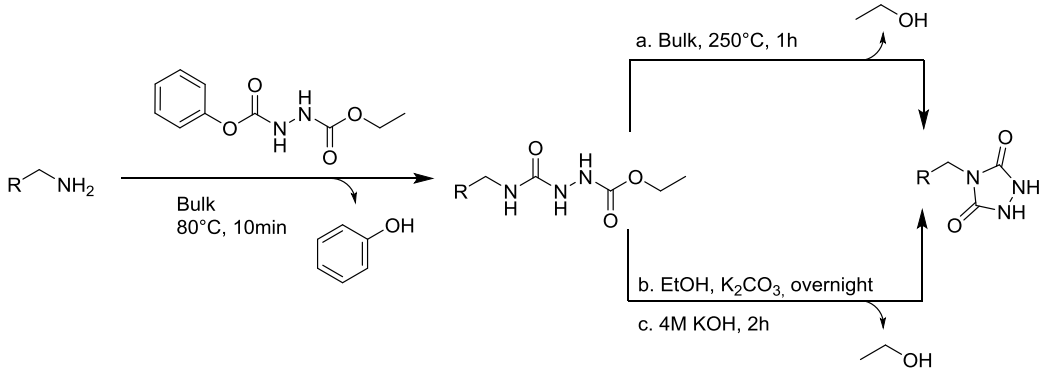

Figure 4: The urazole is obtained in a one-pot reaction via the direct formation of the semicarbazide, which further reacts towards the urazole via a thermal or basic cyclization.

As can be seen in Figure 4, the activated intermediate EPHD is used in the first step to obtain the semicarbazide in one reaction step. In order to synthesize EPHD, Breton *et al.* make use of phenyl chloroformate which is toxic and corrosive. To improve the sustainability, DPC was applied in this synthesis. After an extensive optimization process, the synthesis towards EPHD was performed in bulk at 80 °C with one equivalent of DPC and a twofold excess of EC (Figure 5). Purification of the product, to remove the excess of EC, was performed by precipitation in water. The produced phenol and the excess of EC could in principle be recycled in industrial processes.

As can be seen in Figure 4, the first reaction step was performed in bulk at 80°C, the melting temperature of EPHD, to obtain the semicarbazide. A ^{1}H-NMR analysis showed that already after 5 minutes, full conversion was reached, which demonstrates the fast reaction with the activated intermediate. In the next experiments, the reaction time was kept at 10 minutes to ensure complete reaction. Another advantage of this method was that no urea side product was formed. Therefore, a thermal cyclization was still possible, but not obligated, as a basic cyclization is also a possibility without the need for intermediate purification.

In the last step, the urazole was obtained by thermal or basic cyclization (Figure 4). Just as the first methodology, the thermal cyclization was performed at 250 °C for 1 h under a gentle nitrogen flow to remove the produced phenol. The basic cyclization was applied in the case when thermal cyclization was no option because of the present functionalities. The basic cyclization was performed under milder reaction conditions, by refluxing the semicarbazide overnight in a solution of K_2CO_3 in ethanol. Although this is an effective process, longer reaction times are required. If the synthesized urazole precipitates in water and can withstand harsher reaction conditions, the basic cyclization can also be performed in a 4M KOH solution for 2 hours.

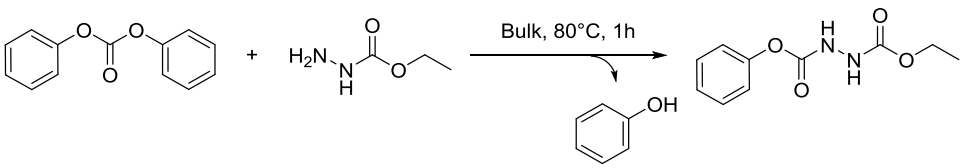

Figure 5: Synthesis of EPHD via reaction between EC and DPC in bulk.

As can be seen in Table I, this methodology was applied to the same amines as in the first methodology. Again, high yields were obtained when no competitive functionalities were present, for example when butyl-, benzyl- and cyclohexanemethylamine, with yields of 89 %, 85 % and 95 % respectively. Breton already showed that aniline was unreactive towards EPHD in solution, which was also the case with our optimized conditions, even at longer reaction times of 24 h. In contrast to the first methodology, the alcohol-functionalized urazole starting from 3-amino-1-propanol could be obtained thanks to the use of the reactive intermediate. Finally, a yield of 78 % was obtained. To obtain a urazole with a thiol end group, cysteamine was used and the synthesis was successful with a lower yield of 27 %. Also a bis-urazole was obtained with ethylene diamine as starting compound. With this methodology, some urazoles were cyclized via a basic cyclization to avoid side product and this was the case for urazoles based on tetrahydrofurfurylamine, 3-amino-1-propanol and cysteamine.

Synthesis of linear polymers

It would be interesting to incorporate the sustainable urazoles in linear polymers and investigate their potential in polymer applications. Because TAD compounds are highly reactive towards dienes and enes via a Diels-Alder of Alder-ene reaction, a linear polymer could be obtained if the TAD compound can undergo an intermolecular reaction with a double bond located in the R-group of the TAD compound. An oxidation of the urazole towards its corresponding TAD compound would then initiate the polymerization. In order to optimize the sustainability of the polymers, renewable starting compounds were selected and the reactions were, where possible, performed via fast, one-pot reaction mechanisms. The color change after oxidation could be employed to follow the reaction from the TAD compound towards the polymer.

Oleylamine

With the urazole synthesized in route A and B, an oxidation with DABCO-Br in DCM was performed (Figure 6c). After oxidation, the reaction mixture was filtered and the filtrate was further stirred overnight (Figure 6d). The azo bond of the TAD compound reacts via an AE-reaction to the double bond of the side chain. The red color became yellow, which indicated that the TAD compound was consumed. A high viscous oil was obtained, with a M_n of 3400 g/mol and dispersity of 1.4 measured on the THF-SEC and DSC analysis shows a T_g of -8°C.

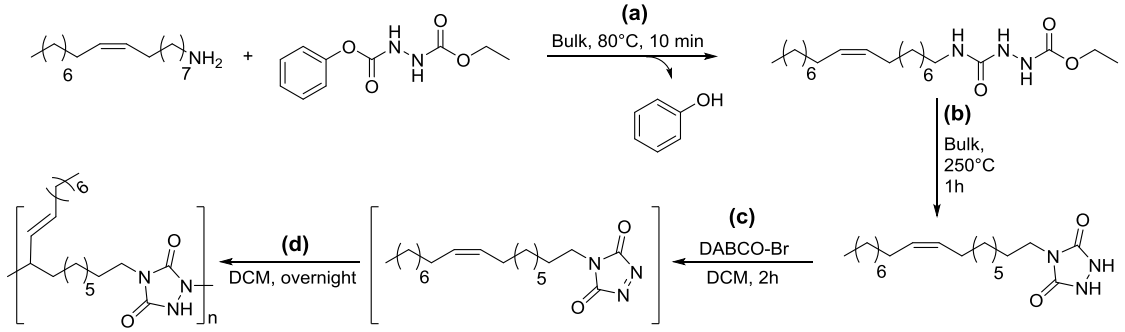

Figure 6: Semicarbazide formation between oleylamine and EPHD according to step 1 of route B and (b) thermal cyclization towards oleyl-urazole. (c) Oxidation of the urazole to the oleyl-TAD compound with DABCO-Br and (d) direct polymerization of the TAD compound to a linear polymer.

Citronellol

To synthesize a urazole with a citronellol side chain, first the alcohol functionality of citronellol should be converted towards an amine functionality. This was done via the Mitsunobu reaction with diethyl azodicarboxylate (DEAD), which resulted in citronellyl amine with an overall yield of 69 %. The second methodology for the urazole synthesis was applied (Figure 8a). The cyclization was performed in 4M KOH (Figure 8b), but next to the urazole, a side product (30 %) was formed (Figure 7). After removal of the side product with a recrystallization, a yield of 58 % of the urazole was obtained. Thereafter, the oxidation with DABCO-Br was performed (Figure 8c) and after filtration, the solution was further stirred overnight at RT (Figure 8d). The red color disappeared, which indicated that all TAD was consumed. DMA-SEC shows a low M_n of 1100 g/mol and a dispersity of 2.6.

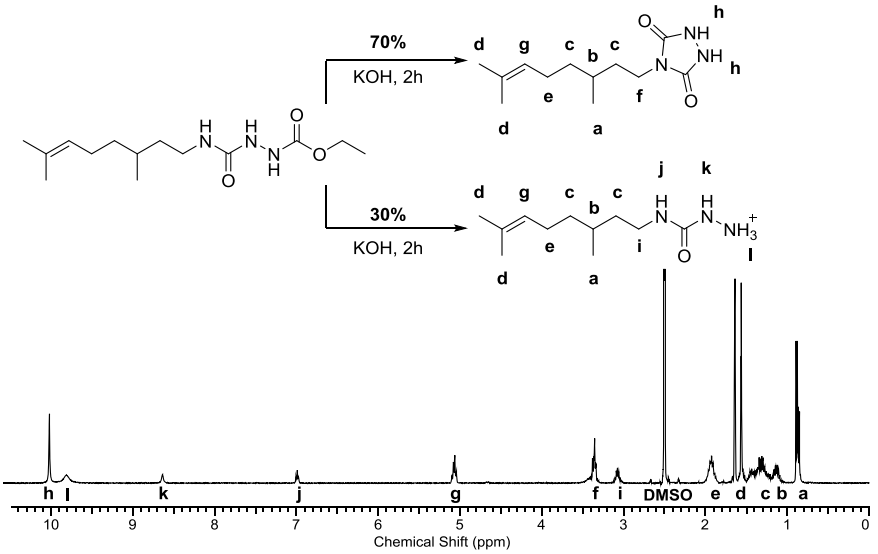

Figure 7: Product and side product of the cyclization of citronellyl-semicarbazide.

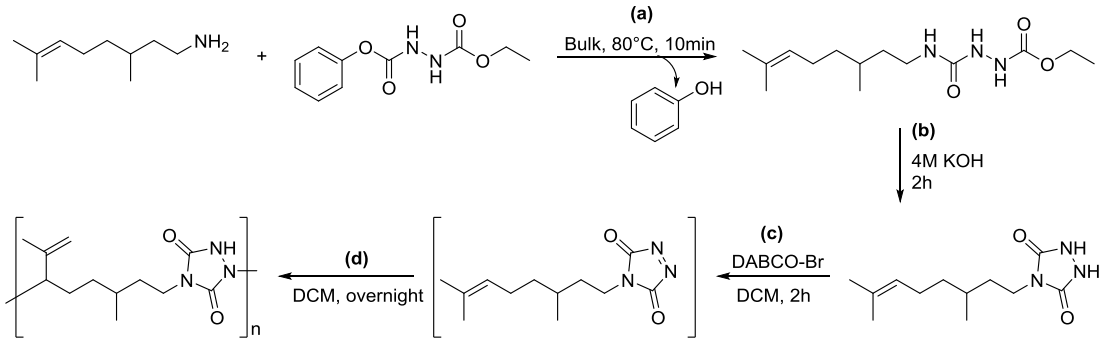

Figure 8: (a) Semicarbazide formation between citronellyl amine and EPHD according to step 1 of route B and (b) basic cyclization in KOH towards the citronellyl-urazole. (c) Oxidation of the urazole to the citronellyl-TAD compound with DABCO-Br and (d) direct polymerization of the TAD compound to a linear polymer.

<u>Synthesis of hyperbranched polymers</u>

The interest in hyperbranched polymers (HPs) is high because of their promising applications[21], but unfortunately, nowadays most of the HPs are based on fossil resources. Parallel to the investigation of citronellol in linear polymers, geraniol is used to obtain HPs.

Geraniol

Again, a Mitsunobu reaction was performed to obtain geranyl amine, with an overall yield of 68 %. The urazole with geranyl amine as starting compound was synthesized via route B with a cyclization in KOH (Figure 9b). In this case, a yield of 53 % was obtained, which was lower than expected because of the purification of the semicarbazide. Again, the polymerization was performed with DABCO-Br (Figure 9c) and after filtration, the reaction further stirred to allow for polymerization towards a HP (Figure 9d). THF-SEC shows that product has a M_n of 580 g/mol with a dispersity of 1.3. Afterwards, DMA-SEC indicates that the HP has a M_n of 1100 g/mol with a dispersity of 1.2. The difference in M_n indicates that the polymer contains hydrogen bonds which makes the radius of the product smaller.

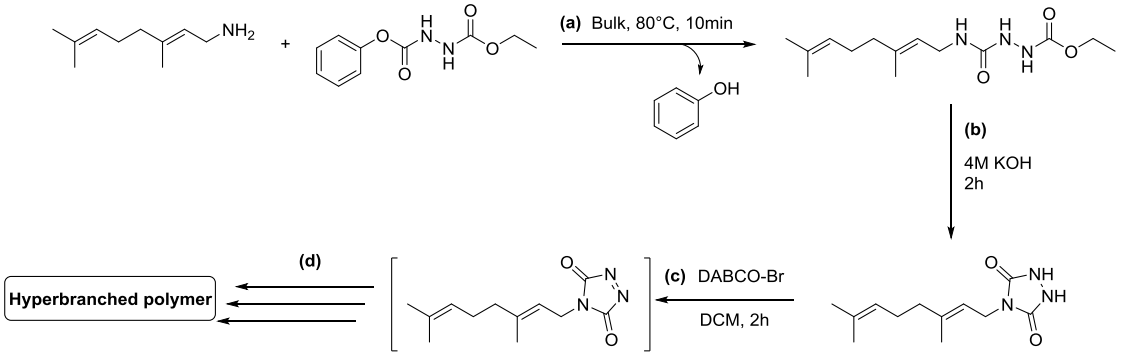

Figure 9: (a) Semicarbazide formation between geranyl amine and EPHD according to step 1 of route B and (b) basic cyclization in KOH towards the geranyl-urazole. (c) Oxidation of the urazole to the geranyl-TAD compound with DABCO-Br and (d) polymerization of the TAD compound to the HP.

Conclusion

It can be concluded that the synthesis towards more sustainable urazoles was successful, as the two one-pot isocyanate-free synthesis routes were optimized and applied to a wide range of amines with different R-groups. Depending on the starting product and desired incorporated functionalities, one synthesis route is preferred over the other. The urazoles with alkyl or related functionalities were perfectly obtained with high yields via the first method, while the second methodology allowed more competitive groups. While the original synthesis routes of Mallakpour and Breton also result in high yields, the synthesis developed in this project are more sustainable, as chloroformates and solvents are avoided and equimolar amounts are applied. Furthermore, the one-pot process enhances the easiness of the syntheses and strongly reduces the reaction time, as the reactions are fast, quantitative and there is no need for intermediate purification.

Linear and (hyper)branched polymers with TAD-adducts in the polymer backbone were investigated with renewable starting materials and via the optimized urazole synthesis route, a sustainable route was achieved as much as possible. The polymers were obtained via a fast, one-pot intermolecular reaction. The low molar mass could be explained by the oxidant DABCO-Br, which can promote bromination of the double bonds. Therefore, it is important to investigate a range of oxidation systems in which self-condensation polymerization can occur *in situ* without side reaction such as bromination or oxidation of the unsaturations. However, we have shown that AB- and AB_2-monomers can be synthesized with the goal to

obtain linear and (hyper)branched polymer structures with strong hydrogen bonding properties in the polymer backbone, which could give rise to interesting polymer applications.

Acknowledgments

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Table of Contents

List of Abbreviations

ADC	azodicarboxylate
ADMET	acyclic diene metathesis
AE	atom economy
AE	Alder-ene
bis-TAD	bisfunctioneel 1,2,4-triazoline-3,5-dione
$CDCl_3$	chloroform-d
CMM	couple-monomer method
d	doublet
$Đ$	dispersity
DABCO	1,4-diazabicyclo[2.2.2]octane
DABCO-Br	tetramer 1,4-diazabicyclo[2.2.2]octanebromide complex
DA	Diels-Alder
DB	degree of branching
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMC	dimethylcarbonate
DMM	double-monomer method
DMSO	dimethylsulfoxide
DMSO-d_6	dimethylsulfoxide-d_6
DPC	diphenylcarbonate
DPPA	diphenyl phosphoryl azide

DSC	differential scanning calorimetry
EC	ethyl carbazate
EPHD	ethyl phenyl hydrazine-1,2-dicarboxylate
HOMO	highest occupied molecular orbital
HP	hyperbranched polymer
IR	infrared spectroscopy
LC-MS	liquid chromatography - mass spectrometry
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
MCM	multi-component method
min	minutes
M_{n}	numeric average molecular weight
M_{w}	weight average molecular weight
N	normality
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
PAMAM	polyamidoamine
PCL	polycaprolactone
PE	polyethylene
PhTAD	4-phenyl-1,2,4-triazoline-3,5-dione
pK_a	acid dissociation constant
PLA	polylactic acid
ppm	parts per million
PS	polystyrene
q	quadruplet
quint	quintuplet
RAFT	radical addition-fragmentation transfer
ROMP	ring-opening metathesis polymerization
RT	room temperature

s	singlet
SEC	size exclusion chromatography
sec	seconds
sext	sextuplet
SMM	single-monomer method
t	triplet
TAD	1,2,4-triazoline-3,5-dione
TBD	triazabicyclodecene
T_g	glas transition temperature
TGA	thermogravimetric analysis
THF	tetrahydrofuran

Chapter I

Introduction and Aim

Nowadays, polymers play a prominent role in our modern life because of their wide applications in packaging, building, safety and electrical devices, as well as in high-end applications such as the medical field and agriculture. Because of the increasing interest in polymers, two large consequences emerged, namely the depleting stock of fossil resources and the growing plastic waste stream, both on land and in the ocean. Figure I.1 indicates that these negative effects will further increase in the future.[1] For example, in 2050, the amount of plastics in the ocean will be larger than the amount of fish by weight. Moreover, the amount of plastics will accumulate because they can remain in the ocean for hundreds of years. Not only the plastic waste will increase, but also its impact on the oil stock. In 2050, 20 % oil will be used in the plastics industry instead of the current 6 %. Furthermore, the production of plastics will grow with 3.8 % per year, while the total oil production is expected to grow with a rate of only 0.5 % per year. Therefore, oil prices are expected to increase, and actions need to be taken to avoid the use of fossil-based materials.

As a result, the awareness to develop more sustainable materials increases in both academia and the industrial world. The challenge we are facing in these uncertain times is twofold. First, the use of renewable resources should be expanded to achieve more sustainable polymers and reduce the consumption of petroleum based resources. Secondly, the possibility towards biodegradation should be further investigated and applied in a broader range of materials. In order to speed up this transition towards bioplastics, new research is required, in which existing processes should be redesigned and optimized again. Nowadays, bioplastics are facing a positive increasing trend, as their production is predicted to grow from 4.16 million tonnes in 2016 to 6.11 million tonnes by 2021 (Figure I.2).[2]

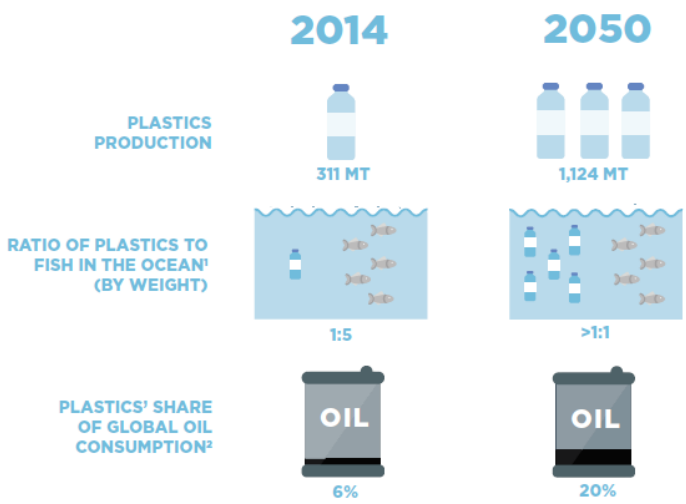


Figure I.1: The plastic volume in 2014 and their forecast for 2050.[1]

Despite the positive trend in the production of bioplastics, they still only represent less than 1 % of the about 300 million tonnes of plastics produced annually.

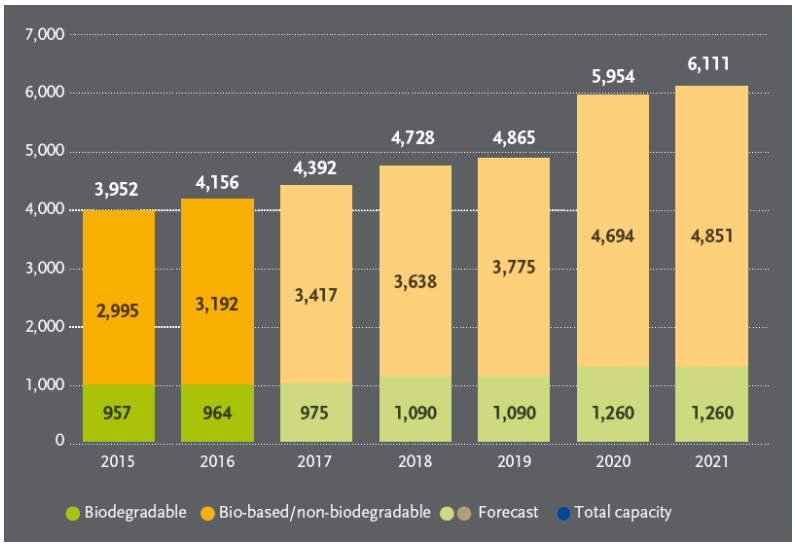


Figure I.2: Global production capacity of bioplastics.[2]

The necessary increase in sustainability pushes researchers all over the globe to show innovation and creativity in order to solve the problems they are faced with. Every day, whole new chemistries are developed and are added to the polymer toolbox. However, sometimes the revival of a chemistry platform can be just as rewarding, as is the case with triazolinedione chemistry. 1,2,4-Triazoline-3,5-diones (TADs) are interesting compounds because their electron poor structure makes them the most reactive dienophiles and enophiles currently known. Because the commercial availability of TAD compounds was limited, their application window was still narrow, while their unique reactivity makes

them extremely useful in the field of green chemistry. A recent publication in Nature chemistry from our research group, concerning TAD chemistry, has triggered the interest of different research groups worldwide, leading to its revival in polymer chemistry.[3] For example, in the field of green chemistry, Türünç *et al.* reported the fast crosslinking of plant oils using bivalent TAD molecules.[4] Furthermore, Tang and co-workers introduced a method to enhance the mechanical strength of plant-oil based thermoplastic elastomers via TAD chemistry.[5] Another application was introduced by Vlaminck *et al.*, who proposed a post-polymerization functionalization method for acyclic diene metathesis (ADMET) derived polymers by using TAD.[6] Furthermore, sustainable applications in shape memory materials can be found.[7]

However, the synthesis towards the stable TAD-precursors, namely urazoles, nowadays starts from the corresponding isocyanate, as described by Cookson in 1971.[8] Not only are isocyanates limited in structural diversity, they are also very toxic. To avoid the use of these hazardous compounds, researchers already improved the sustainability by using carboxylic acids and amines as starting materials.[9–12] However, the remaining steps in the synthesis towards the urazoles still limit the sustainability, as the use of the toxic diphenyl phosphoryl azide (DPPA) and chloroformates is a main drawback of these reaction routes. Therefore, the aim of this project was in a first step, to improve the sustainability of the amine-based urazole synthesis.

In a first part of this project, the synthesis towards the TAD-precursor is optimized in terms of sustainability and efficiency. Two routes will be investigated with their own advantages and disadvantages. As starting compound, a wide range of amines will be tested with different functionalities. After overcoming the lack of availability of the TAD compounds and their burdensome, harmful synthesis in the first part of this project, the TAD compounds will be tested in polymer applications. First, the synthesis of linear polymers with urazoles in the backbone will be investigated. Furthermore, as the use of TAD compounds has never been investigated in hyperbranched polymers (HPs), the unique reactivity of the TAD compounds will also be exploited to obtain HPs. As sustainability is a focus point of this master research, the synthesis towards polymers will start from renewable starting materials with a focus on fast, one-pot reaction mechanisms.

Chapter II

Theoretical Background

II.1 Green chemistry

II.1.1 Introduction

Plastics have become an essential part of our everyday life, as can be seen in the production volumes, which have surged over the past 50 years. While the production only reached 15 million tons in 1964, this increased to 322 million tons in 2015 and is expected to double over the next 20 years.[2] This increase in production volume can be attributed to the broad application window of plastics, ranging from packaging, building and construction to electrical devices and many others. Packaging represents the largest share of the total volume. In Europe, for example, this volume amounted to 39,9 % in 2015 (Figure II.1).[13]

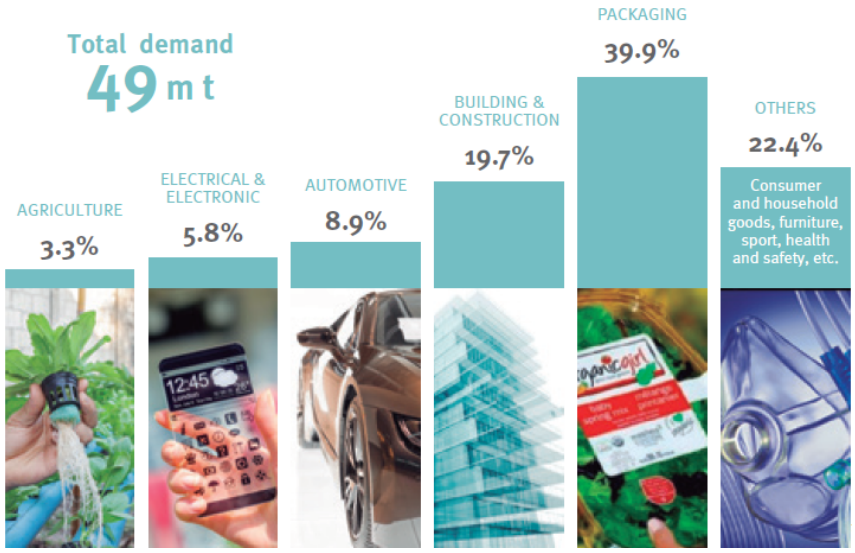


Figure II.1: Distribution of European plastics demand by segment in 2015.[13]

The increasing interest in plastics over the years has two large consequences, namely the depleting stock of fossil resources, particularly petrol and natural gas[14] and the growing plastics waste stream.[1] First, the high mining rate induces the exhaustion of fossil resources, which is predicted within a few decades.[15] This leads to the increased awareness when it comes to sustainability of products, both on the industrial and the governmental level. The second issue concerning the multitude of plastics is the enormous accumulation of plastics, not only on land, but especially in the ocean. The ocean can hold plastics for hundreds of years[1] and includes nowadays more than 150 million metric tons of plastic waste.[16] If the mentality of the people does not change before 2050, it is predicted that there will be, by weight, more plastics in the ocean than fish.[1]

The above mentioned difficulties, being the dwindling of fossil resources and the multitude of waste, have become a significant problem and therefore, actions need to be taken. In the ideal case, plastics would re-enter the circular economy as technical or biological nutrients instead of being disposed of.[1] To achieve this, increasing attention is going to the development of more sustainable plastics, which are derived from renewable resources or can undergo biodegradation.

The transition to more sustainable polymers, however, proceeds slowly, as this requires new research and investments, where polymers based on fossil resources are already widely examined and their processes are perfectly optimized. Processes have to be redesigned and optimized again, and on top of that, the sustainable polymers should satisfy some conditions. The polymers must have a low cost, lower or equal to the fossil resource equivalent, as companies will not be eager to invest in more expensive products and they must also have the same mechanical and physical properties. This shows why the integration of sustainable solutions in the society goes rather slow.

II.1.2 Definitions

In 1987, sustainability was defined by the Brundtland commission as follows:

"Sustainability implies meeting the needs of the present without compromising the ability of future generations to meet their own needs."[17]

Following the definition of sustainability, the term "Green Chemistry" arose in the beginning

of the 1990s, which was defined as "the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances".[18–20] It should be noted that sustainable and green chemistry are frequently interchanged and are often used in the same context. Green chemistry covers every possible aspect of chemistry, including macromolecules and polymers, which will be the focus of this manuscript and are often described as "biopolymers".

When biopolymers are considered, two different factors are important, namely their origin (biobased or fossil-based) and their biodegradability (Figure II.2).[21] A polymer is biobased if the product has been made from renewable resources. A biodegradable polymer, however, does not need to be build up out of renewable resources but has the characteristic to degrade into low molecular weight compounds like CO_2, CH_4, H_2O and biomass under the influence of chemical, physical and/or biological stimuli.

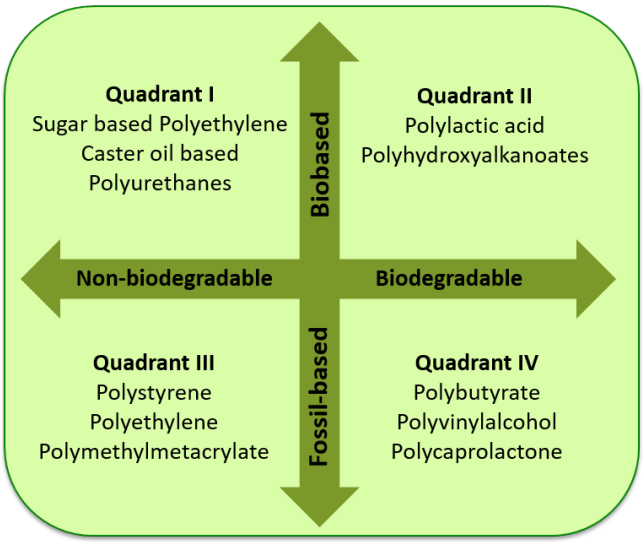


Figure II.2: Examples of different plastics related to their origin and biodegradability.

It can thus be concluded that not every biobased material is also biodegradable and vice versa. For example, the conventional production of polyethylene (PE)[22] is based on fossil resources and PE is thus not biobased nor biodegradable. As can be seen in Figure II.2, this positions conventional PE in the third quadrant. On the other hand, this conventional way of producing PE is not the only method, as PE can also be generated from sugars, which makes the polymer biobased (quadrant I).[22] On the other hand, a polymer like polycaprolactone (PCL) can be degraded by specific bacteria, therefore, it can be placed in quadrant IV.[21] An example of a polymer located in the second quadrant of Figure II.2,

which is both biobased and biodegradable, is polylactic acid (PLA).[22–24] The monomer of PLA is generated by bacteria, which makes the polymer biobased. The biodegradable PLA decomposes slowly in H_2O, CO_2 and humus.[25]

II.1.3 Twelve principles of green chemistry

In 1998, P. Anastas created a cohesive set of 12 principles, which should be a guiding framework to obtain a more green chemistry-based industry (Figure II.3).[18,19] These principles should be applied to all industry sectors, such as aerospace, cosmetics, energy, etc... in order to target maximal sustainability.

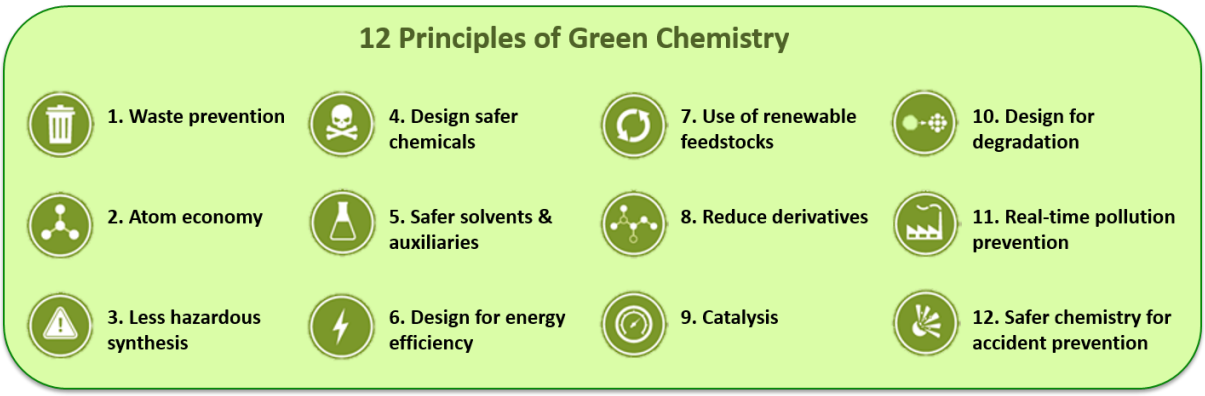


Figure II.3: The "12 Principles of Green Chemistry" as postulated by Anastas.[18,19]

The first principle postulates that it is always better to prevent waste than treating it afterwards. In 1992, R. Sheldon introduced the Environmental Impact Factor which represents the actual amount of waste formed per kilogram in a process (Equation II.1).[26] This value should be minimized in sustainable processes.

$$\text{E factor} = \frac{\text{weight of waste}}{\text{weight of desired product}} \tag{II.1}$$

Furthermore, in order to avoid waste, the atom economy (AE), as defined in the second principle (Equation II.2), should be optimized. This could be realized by selecting raw materials and reaction pathways in such a way that the maximum number of atoms from the reactant is incorporated in the final product. Ideally, all of them are inserted.

$$\text{Atom economy (AE)} = \frac{\text{MW product}}{\text{MW reactants}} \tag{II.2}$$

For example, Diels-Alder type reactions have an AE of 100% since all atoms from the reactant are incorporated in the final product. The use of less hazardous chemical synthesis is beneficial, combined with the design of safer chemicals and use of safer solvents and auxiliaries. If these last ones are used, they should be innocuous. Next to waste products, unutilized energy can also be considered as waste. Therefore, energy requirements of chemical processes should be minimized. If possible, reactions should be performed at ambient temperature and pressure. Maybe the most important principle for our research, is the use of renewable feedstock or material, in order to avoid the depletion of the petroleum feedstock and natural gas. The next principles include the avoidance of unnecessary derivatizations and the use of catalytic reagents instead of stoichiometric reagents, in order to further avoid waste creation. Afterwards, end-of-lifetime products should be biodegradable so that they do not retain in the environment but degrade into innocuous degradation products. Furthermore, real-time analysis needs to be developed and applied in order to prevent pollution. Finally, inherently safer chemistry should be chosen to minimize the potential for chemical accidents.

II.1.4 Renewable resources

II.1.4.1 Lactic acid

Lactic acid is an α-hydroxy acid and is a renewable resource derived from corn or sugar beets.[22] First, starch is enzymatically hydrolyzed to glucose, which is further converted into D- or L-lactic acid by Lactobacillus. Lactic acid can subsequently undergo condensation with formation of the cyclic lactide dimer, followed by ring opening polymerization to form polylactic acid (PLA) (Figure II.4).

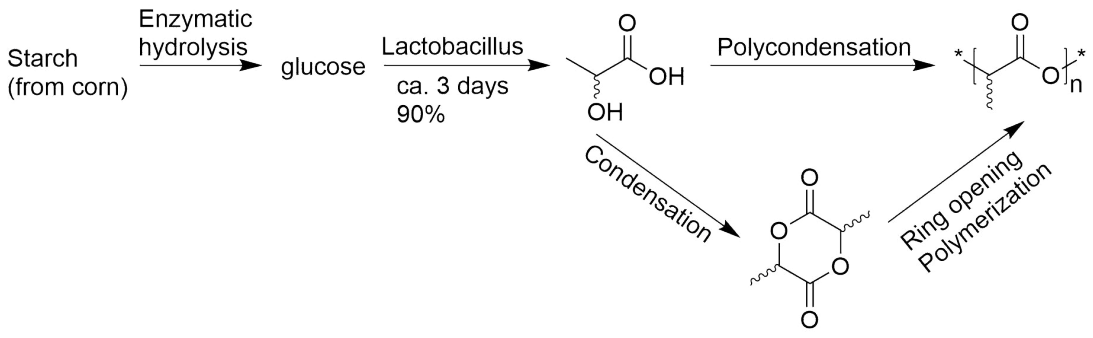


Figure II.4: Synthesis of polylactic acid starting from starch.

PLA is a thermoplastic aliphatic polyester that is located in the second quadrant of Figure II.2. It decomposes in H_2O, CO_2 and humus but due to the hydrophobic character, the degradation rate is very slow.[25] An advantage of PLA is its biocompatibility, which means it can be used in biomedical applications.[27,28] On top of that, PLA has a better thermal processability compared to other biopolymers.[29] Injection molding, blow molding, film extrusion, fiber spinning are some of the used processing methods. The total production process of PLA requires 25 to 55% less energy compared to petroleum-based polymers.[30] However, it is a very brittle material with less than 10% elongation at break[31,32] and the absence of reactive side groups results in limited post-modifications options.[24]

Despite the disadvantages, PLA has already found a lot of applications in paper coating, films, packaging, textile industry and biomedical implants for growing living cells.[21]

II.1.4.2 Ethylene

Usually, the monomer ethylene is derived from steam cracking of naphtha or ethanol dehydration.[33] However, ethylene can also be deduced from starch corps.[34] In this case, the starch is hydrolysed into glucose or other sugars, which are further fermented to bio-ethanol. Finally, catalytic dehydration turns the bio-ethanol into ethylene. The production of polyethylene is performed using a catalyst. Conventional and bio-based polyethylene have the exact same properties as only the source of the monomer has shifted from a fossil to a renewable resource. Switching from quadrant 3 to quadrant 1 in Figure II.2 is a favourable evolution in sustainability. The application of polyethylene ranges from film applications to packaging, bags and tubes.[22]

II.1.4.3 Natural oils

Natural oils exist essentially of a mixture of mono-, di- and triglycerides which are obtained via a reaction of glycerol and fatty acids.[35] Oils are obtained from plants like linseeds, sunflowers, olives, ... and the properties of the different natural oils differ tremendously because of the different distribution of fatty acids. Examples of fatty acids are palmitic acid, stearic acid and oleic acid with each its own physical properties. The triglyceride castor oil contains mainly unsaturated ricinoleic acid (87.5 %), oleic acid (5 %), linoleic acid (4 %) and palmitic acid (1.5 %).[35] As ricinoleic acid contains an alcohol group, the multitude of hydroxyl groups present in castor oil can react with diisocyanates to form polyurethane

networks (quadrant I of Figure II.2).[36,37] Applications are found in the biomedical industry because of its biocompatibility and sometimes also its biodegradability.[35] As a final example, the paint industry makes use of polyamides based on tall and soybean oils.[38]

II.1.4.4 Terpenes

Terpenes can be classified as one of the largest families of naturally-occurring compounds, with a multitude of structural diversity.[39] They are found in essential oils, produced by plants, which makes them a renewable raw material. They also occur in nature as secondary metabolite compounds and are synthesized by marine microorganisms, fungi and some insects. In nature, terpenes are used as pheromones, flavors, fragrances and nutrients, while mankind implements them in a broad range of applications, including the treatment of different diseases, such as cancer.[40] In 1953, Ruzicka and Wallach found that the carbon skeleton of terpenes can be described as repeating units of isoprene $(C_5)_n$, which is the reason why terpenes are also denoted as isoprenoids.[41] The units of isoprene are ordered in a regular pattern, which can be head-to-tail, to form linear structures, or in a circular manner. When n > 8, the structure is called a polyterpene. Figure II.5 shows some examples of terpenes.

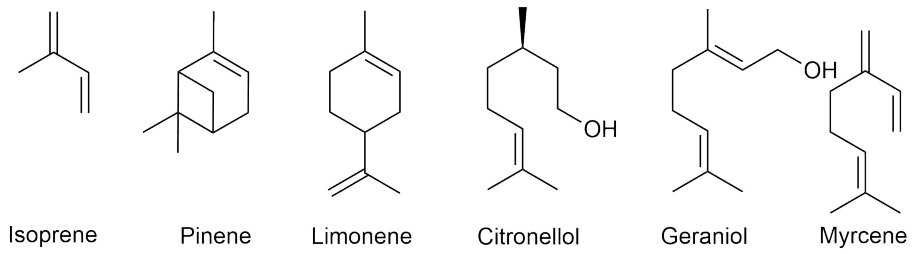


Figure II.5: List of a few terpenes.

For example, terpenes have been used in polymer chemistry to form hyperbranched polymers via a ring-opening metathesis polymerization (ROMP) of dicyclopentadienes with terpenes.[42] Other interesting polymeric materials are copolymers of terpenes with conventional monomers like for example controlled reversible addition fragmentation chain-transfer (RAFT) systems involving β-pinene and acrylic comonomers.[43] Also free radical co-polymerizations of terpenes and monomers like styrene and methyl methacrylate, show some great success.[44] In this manuscript, terpenes are useful as monomers because of the numerous unsaturations present in the structure, which can be exploited for Alder-ene reactions with 1,2,4-triazoline-3,5-diones (*vide infra*).

II.2 1,2,4-Triazoline-3,5-diones

II.2.1 Introduction

1,2,4-Triazoline-3,5-dione (TAD) is a heterocyclic azodicarboxylate. Azodicarboxylates (ADC's) can be defined with the general formula R-CO-N=N-CO-R'. An azo bond generally shows a high reactivity, because of the lower energy of the lowest unoccupied molecular orbital (LUMO). In ADC's, this effect is further enhanced by the two carbonyls which give an extra inductive electron-withdrawing effect that further lowers the energy of the LUMO. For TAD, this results in fast and high-yielding reactions towards the desired reaction products.[45–47] Because of the high reactivity of the TAD compounds, their bench stability is limited. Therefore, a TAD-precursor urazole (1,2,4-triazolidine-3,5-dione) is synthesized first, which is only oxidized towards the corresponding TAD molecule when needed (Figure II.6).[48] It should be noted that the two N-H protons of the urazole are rather acidic with pK_a of 4.71.

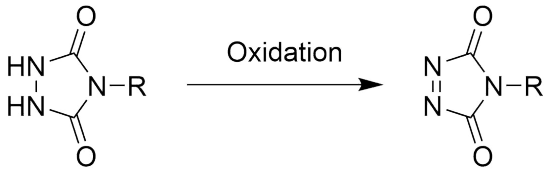


Figure II.6: Oxidation of the urazole towards the corresponding TAD compound.

As discussed above, TAD molecules show a unique reactivity, which makes them very reactive dienophiles and enophiles. An extra advantage of the conjugated π-system is that TAD shows a distinct red color, which provides a visual feedback mechanism because the red color disappears upon reaction and makes the progress straightforward to follow.

In the next paragraphs, the most relevant synthesis routes towards TAD compounds, their reactivity and applications will be provided. A more extensive review on both the synthesis and applications of TAD can be found in a recent review article from our research group.[49]

II.2.2 Synthesis

Because TADs are synthesized by the oxidation of the corresponding urazole, synthesis of this urazole is elaborated here. The oldest routes for urazole formation were based on hydrazodicarboxamide intermediates.[50] This synthesis route involves a couple of limitations

like low yields and harsh reaction conditions. Therefore, the synthesis route discussed in the next paragraphs follows the more favorable route that starts with the synthesis of semicarbazides (II.2.2.1). The second step includes the ring closure of the semicarbazide to the urazole (II.2.2.2). In a final step, oxidation of the urazole towards the corresponding TAD molecule is discussed (II.2.2.3).[49]

II.2.2.1 Semicarbazide

In 1961, Zinner and Deucker proposed a synthesis scheme based on 1-alkoxycarbonyl semicarbazides under mild conditions.[51] Starting from isocyanate and ethylcarbazate, 4-substituted ethoxycarbonyl semicarbazides were synthesized and after cyclization, 4-phenyl- and 4-butyl-urazole were obtained. This would later become known as the Cookson synthesis, as it was in 1971 that Cookson and co-workers published the complete synthesis procedure of 4-phenyl-TAD (PhTAD) starting from hydrazine, diethyl carbonate and phenyl isocyanate (Figure II.7).[8]

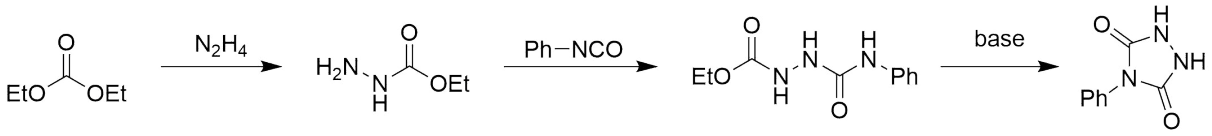


Figure II.7: Synthesis of 4-phenyl-urazole by Cookson in 1971.[8]

Cookson used phenyl isocyanate to obtain PhTAD but the side group could be varied when different isocyanates were applied. The disadvantage of this synthesis route is the lower availability of isocyanates and their toxicity.[52] Because of the low availability, isocyanates could also be formed in situ[11] for example via a Curtius rearrangement with the aid of diphenylphosphoryl azide (DPPA).[11,12,53] An isocyanate-free synthesis route that makes use of less toxic, readily available and less expensive starting materials is however recommended. Examples of these less toxic starting materials are found in anilines and primary amines.[9] Two main reaction paths can be described.

The first route to synthesize a semicarbazide from an amine, transforms the amine in a carbamate using a chloroformate. In the second step, ethyl carbazate reacts with the reactive carbamate, forming the corresponding semicarbazide (Figure II.8a).[9,54] An example was shown by Mallakpour, who developed a straightforward and efficient route for the synthesis of 4-substituted phenyl derivatives of urazoles starting from anilines.[9,54] The

carbamate was obtained with 4-nitrophenyl chloroformate. After isolation of the carbamate, ethyl carbazate was used for the second step to form the semicarbazide. Afterwards, Barbas and co-workers designed a one-pot reaction by using an excess of chloroformate and ethyl carbazate, which immediately results in the corresponding semicarbazide.[55–57]

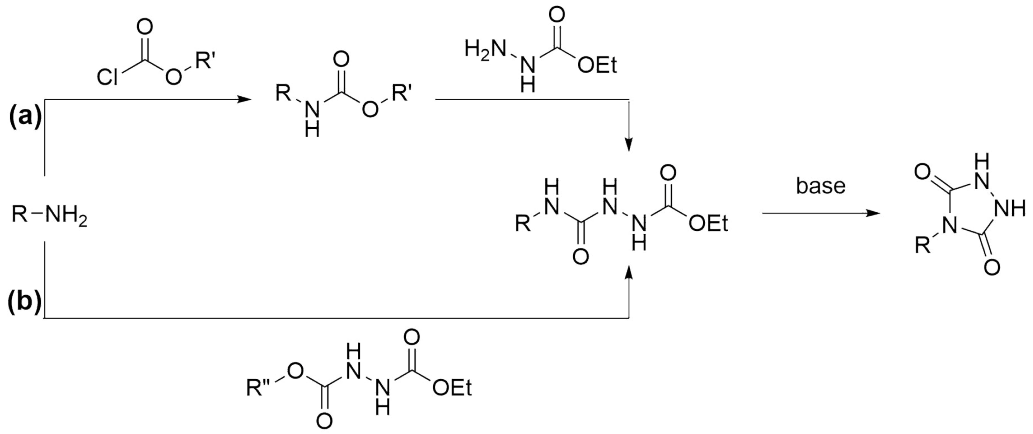


Figure II.8: Synthesis of urazoles with amine as starting products with R'=Et[54], $PhNO_2$[9] and R"=Ph.[10]

The second method was introduced by Breton and Turlington in 2014 (Figure II.8b).[10] Here, the semicarbazide was synthesized via a reactive intermediate, ethyl phenyl hydrazine-1,2-dicarboxylate (R" = Ph). This intermediate was made out of phenyl chloroformate and ethyl carbazate and can react with a range of amines under mild conditions. High yields were obtained, however, purification via column chromatography was needed.

II.2.2.2 Cyclization

The formation of an urazole requires the cyclization of the semicarbazide as can be seen in Figure II.8. Cyclization is mostly performed in mildly basic conditions in a protic solvent.[51,58] Usually, an aqueous potassium hydroxide solution is used at reflux temperatures for 2 to 3 hours, resulting in a solvated urazolyl anion.[8] The urazole precipitates after acidification to pH $\approx$ 1-2 in quantitative yield. A possible side reactions that can occur when the 4-substituted R-group of the semicarbazide is highly electron withdrawing, is the hydrolysis of the hydrazine carboxylate, followed by decarboxylation.[59,60] However, despite this predictable side reaction, the aqueous cyclization is still the most performed method in case of urazoles with an aromatic substituent.

A second widely used method for cyclization uses sodium ethoxide in refluxing ethanol.[59,60] This is a milder process, which also results in high yields and the isolation of the urazole

is completed in a non-aqueous work-up, but the main disadvantage is the longer reaction times of 24 hours. Sodium ethoxide is mostly used when the substituent on the urazole prevents its precipitation. A third similar method is based on the use of potassium carbonate as a base in an aqueous or alcoholic solvent, which also results in higher yields, but again longer reaction times are required.[59–61]

II.2.2.3 Oxidation

For the synthesis of a TAD molecule, the corresponding urazole should be oxidized, which is not always a straightforward process (Figure II.6). This is because of the reactivity of the product, the chemoselectivity of the oxidant and the challenging isolation of TAD reagents. As a manifold of oxidation methods exists,[49] a successful oxidation for every compound can be found. As it is impossible to discuss all methods in detail here, only two oxidation methods that are frequently used in our research group will be described below.

The first method to convert urazoles in their corresponding TAD molecule, makes use of dinitrogen tetraoxide (N_2O_4).[62] N_2O_4 is in equilibrium with nitrogen dioxide (NO_2) and is a liquid below 20 °C.[63] The gas is toxic and instead of handling it in its pure, concentrated liquid form, a less hazardous handling procedure could be created when a solution of the gas in an inert solvent is used.[62,64] After reaction with the excess oxidant, the solvent is evaporated, which result in a residue that still contains little contaminants. After a twofold sublimation of the residue, pure triazolinediones can be gathered.[49]

In 2008, Zolfigol *et al.*, described different oxidants which generate active bromine in situ.[65] An effective oxidant used in this project is the tetrameric complex 1,4-diazabicyclo[2.2.2]octane-bromide (DABCO-Br)(Figure II.9).[48] This heterogeneous oxidant is easy to synthesize and the work-up after the oxidation consists of filtration of the DABCO. The oxidation occurs at room temperature under inert atmosphere for 2 hours.

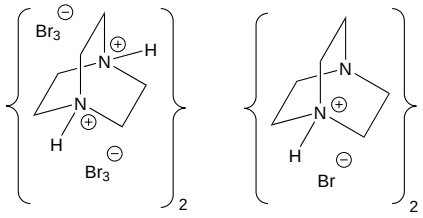


Figure II.9: Tetrameric complex of 1,4 diazabicyclo[2,2,2]octane-bromide.

II.2.3 Reactivity

II.2.3.1 Diels-Alder reaction

In 1928, O. Diels and K. Alder reported the Diels-Alder reaction (DA-reaction). This concerted reaction forms a [4+2]-cycloadduct starting from an electron rich conjugated diene and an electron poor dienophile.[66,67] The reaction products are predictable because of the high stereo- and regioselectivity of DA-reactions.

Next to the formation of regular carbon-carbon bonds, also hetero-DA-reactions are possible. In 1967, Cookson and co-workers reported a DA-reaction between cyclopentadiene and PhTAD, which showed the potential of TAD molecules as strong dienophiles.[68] The DA-reaction between a diene and a TAD molecule (Figure II.10a) is possible because of the low energy gap between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the TAD molecule. As mentioned above (II.2.1), the LUMO of TAD molecules is lowered by the inductive electron-withdrawing effect of the two carbonyl groups and the azo bond, which results in an increased reactivity toward dienes. Therefore, even reactions with less reactive dienes proceed rapidly at room temperature.[69]

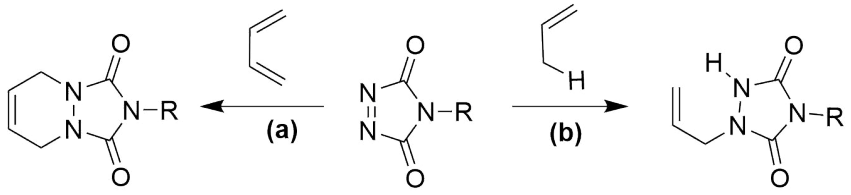


Figure II.10: (a) DA-reaction between TAD and a diene (b) AE-reaction between TAD and an ene.

It has been reported that TAD molecules react 30 000 and 2 000 times faster in a DA-reaction than ethyl azodicarboxylate[70,71] and maleic anhydride[72], respectively. A final advantage of DA-reactions is, like already postulated in II.1.3, the 100 % atom efficiency, which makes this reaction pathway interesting for green chemistry applications.

II.2.3.2 Alder-ene reaction

In 1943, Alder reported an ene-adduct starting from an alkene bearing an allylic hydrogen (ene) and an enophile.[73] Alder-ene reactions (AE-reactions) have an unfavorable activation

entropy, resulting in high activation energies and therefore often require high reaction temperatures and pressure. While intramolecular ene-reaction can be successful at lower temperatures when a Lewis acid catalyst is used, this is not the case for intermolecular reactions.[74]

However, when TAD as highly reactive enophile is introduced, intermolecular reaction can be performed at room temperatures (Figure II.10b). In 1967, Pirkle and Stickler reported this reaction, between an ene and methyl-TAD with formation of the N-allyl-urazole adduct.

Reaction of cyclohexene happens 30 000 times faster with TAD than with ethyl azodicarboxylate.[68] Reaction times could be enhanced when the HOMO of the ene is increased.[49] In AE-reactions, this could be realized by an increased alkylation of the double bond. This was already reported by Butler and co-workers in 1980 and is explained by the electron donating effect of the alkyl chains.[75] This effect can be so strong that a tetra-substituted double bond has about the same reaction time as some conjugated dienes.[76] The shift of the double bond in AE-reaction towards the allylic position on the carbon chain rather than consummation of it, makes this reaction interesting for multiple functionalization or the use in dendrimers (*vide infra*).

II.2.3.3 Side reactions

As mentioned above, TAD is a very reactive compound towards multiple substrates. The consequence of this reactivity is that TAD is also sensible to side reactions (Figure II.11).[49] In most cases, these side reactions are limited, as the desired reaction (DA- or AE-reaction) goes faster. Because of these side reactions, TADs are always stored in a dark, dry medium below room temperature.

The first important side reaction is the hydrolysis under the influence of water. This results in the urazole and amine (Figure II.11a).[69] Attention should be paid when acids or bases are present, because these can accelerate the hydrolysis.[49]

The formation of amines in the above mentioned hydrolysis results in an auto-accelerated degradation of TAD as amines can also induce a side-reaction with TAD. In the case of primary and secondary amines, a nucleophilic attack on the TAD molecule, results in a

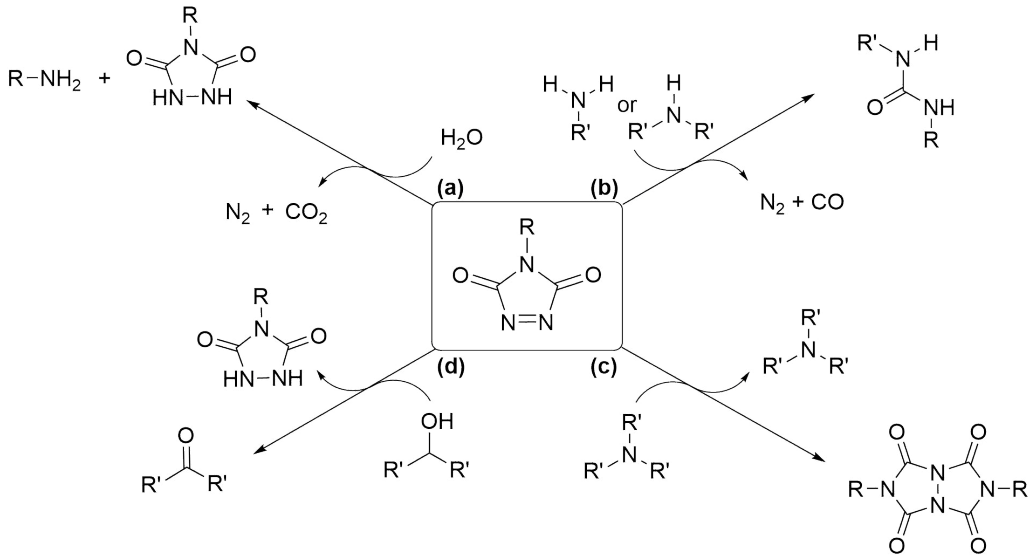


Figure II.11: Important side reactions involving TAD. (a) Hydrolysis, (b) reaction with primary or secondary amines, (c) reaction with tertiary amines and (d) oxidation of alcohols to aldehydes or ketones.[49]

ring-opened species, which can form urea after ejecting N_2 and CO gas (Figure II.11b).[77] Reaction of TAD with a tertiary amine induces an addition of a second TAD molecule after the ring opening and after elimination of the tertiary amine, a dimer is formed (Figure II.11c).[78]

TAD compounds can also act as oxidants and oxidize alcohols to their corresponding ketones or aldehydes (Figure II.11d).[79] A similar oxidation reaction can occur when thiols are present, with the formation of disulfides. The presence of alcohols and thiols in the reaction mixture should therefore be avoided.

II.2.4 Applications in polymer science

The first example of polymer applications of TAD was reported by Pirkle and Stickler in 1970.[80] A colorless polymer of 4-butyl-TAD with an all-nitrogen backbone was obtained via homopolymerization of TAD-based monomers under the influence of a halogen lamp. However, the life time in the original solution was limited and homopolymerization of aromatic TAD compounds was proven to be impossible. From this moment forward, a multitude of polymer applications has arisen.

Most of the polymer applications in the 1970s and 80s were focused on the modification of polydienes by TAD.[81–83] In 1979, G. Butler and co-workers reported an AE-reaction between

polybutadiene and TAD (Figure II.12).[84] The reaction happens at low temperatures and results in high yields. As mentioned before, the double bond is not consumed during the AE-reaction, but shifted to a next position. The modification degree can range from 5 till 100 % and an increase in glass transition temperature (T_g) is observed. The increase in polarity makes the modified polymers soluble in polar solvents. Furthermore, when bifunctional TAD compound were used, crosslinked networks could be obtained.

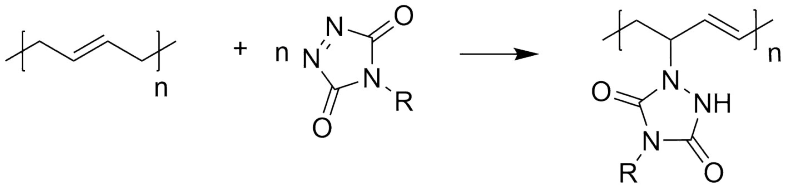


Figure II.12: Reaction between polybutadiene and TAD via an Alder-ene reaction.[84]

The large potential of TAD chemistry, has however been limited by the scarce commercial availability of the building blocks.[85–87] A recent publication in Nature chemistry from our research group, has piqued the interest of different groups worldwide, leading to a revival of this chemistry platform.[3] In the field of green chemistry, a fast crosslinking was reported between plant oils and bivalent TAD molecules.[4,88] Furthermore, the mechanical properties of plant oil-based thermoplastic elastomers could be enhanced by using the strategy of Tang and co-workers[5], who increased the tensile strength of a soybean based thermoplastic elastomer without loss of elongation. A final application was introduced by Vlaminck *et al.*, who proposed a post-polymerization functionalization method for acyclic diene metathesis (ADMET) derived polymers by using TAD.[6]

II.3 Hyperbranched polymers and dendrimers

II.3.1 Introduction

Over the years, a multitude of macromolecular structures has been prepared, ranging from linear polymers to crosslinked networks and dendritic polymers. These dendritic polymers can be described as three-dimensional (3D) highly branched macromolecules with a functional surface.[89] They can be divided in dendrimers, hyperbranched polymers, dendrigrafts and dendronized polymers (Figure II.13).[90]

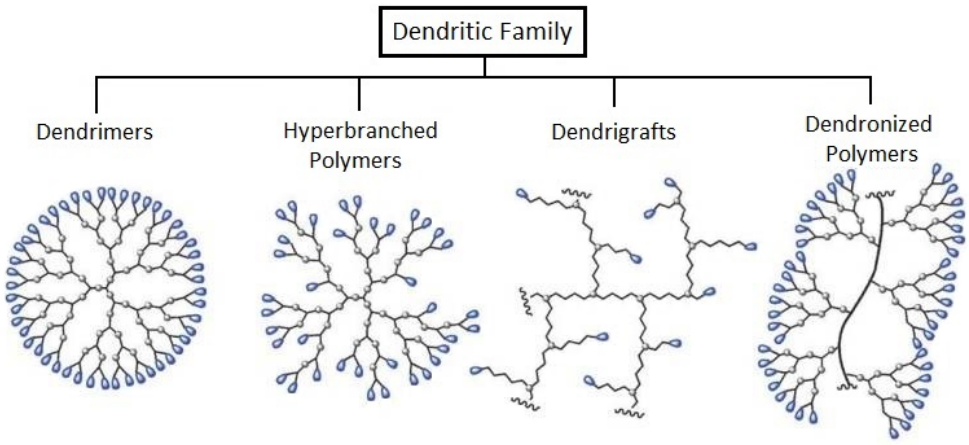


Figure II.13: The four classes of dendritic polymers.[90]

In 1980, dendrimers were first introduced by Tomalia and co-workers[91] and were defined as perfectly branched structures with functional end-groups, in which a single core is surrounded by layers of repeating units which are radially branched. Every layer is referred to as a generation (Figure II.14).[90]

The synthesis of dendrimers is based on step-growth polymerizations and results in a degree of branching (DB) of 1, a higher density and solubility and lower viscosity compared with linear polymers. The dispersity (Đ) is lower than 1.05. A disadvantage of dendrimers is its multi-step synthetic pathway which requires iterative purification, protection and deprotection.[92] These iterative steps can, however, be facilitated by the introduction of click chemistry.[93,94]

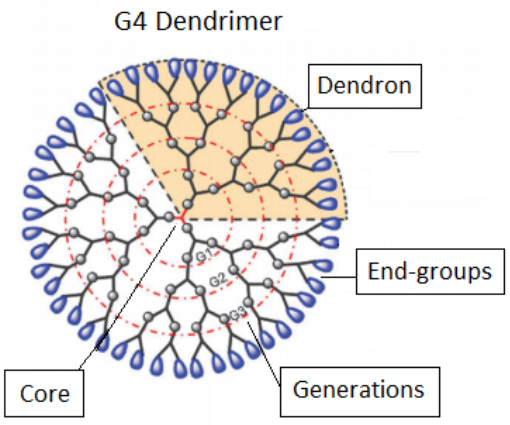


Figure II.14: Different structural components of the dendrimer.[90]

Hyperbranched polymers (HPs) represent another class of the dendritic polymers and differ from dendrimers because of their irregular branching topology and the fact that they do not grow from a central core.[95] HPs consist of three types of structural units namely dendritic, linear and terminal units.[90] Functional groups are located both on terminal and linear units.[96] HPs can be easily synthesized via a one-step process starting from monomers with an AB_x functionality, with x > 1 (*vide infra*). Because of the uncontrolled polymerization, a dispersity of 2 or higher is obtained and the degree of branching typically varies between 0.4 and 0.6. Just like dendrimers, HPs have also higher solubility than their linear analogues because of the many functional end-groups. Furthermore, a lower viscosity and higher density is often observed.

II.3.2 Synthesis

II.3.2.1 Dendrimers

As mentioned above, the synthesis of dendrimers is very time-consuming because of the repetitive stepwise growth and deprotection and activation steps with a purification between every step.[92] Two general synthesis strategies are described, namely divergent and convergent synthesis.[97]

Divergent

The divergent growth strategy starts from a multifunctional core with a multiplicity higher than 2, from which generation by generation is built (Figure II.15).[98] Every reactive group of the core molecule is the start of a dendron (Figure II.14). The first generation (G1) is formed by the stepwise addition of a branching unit AB_x. Here, the protected B-functionality avoids reaction between an A-functionality and a B-functionality of the current generation. After reaction, a purification should be performed to remove side products, unreacted starting materials and defect dendrimers, often via column chromatography. Next, deprotection of the B-functionality is executed, whereupon the second generation could be formed with the same series of steps. This process is repeated until the desired generation is achieved, however, when a higher generation is synthesized, a larger excess of monomers and reagents is required. Incomplete derivatizations also increase with increasing generations. In 1985, Tomalia was the first to report the divergent construction of polyamidoamine (PAMAM) dendrimers.[99]

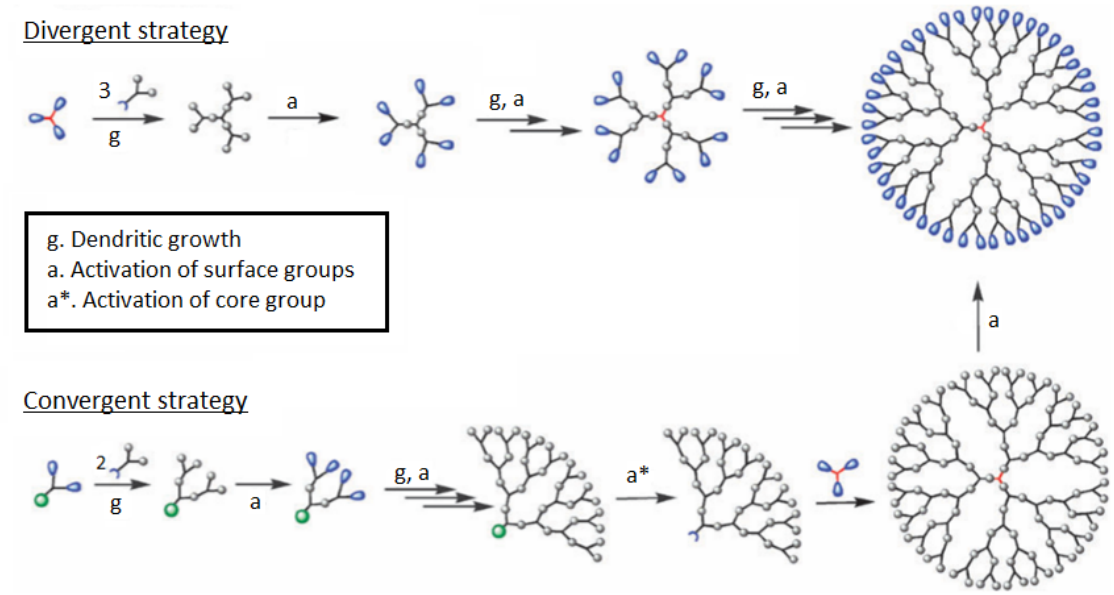


Figure II.15: Divergent and convergent synthesis strategies.[90]

Convergent

The convergent synthesis approach was first reported by Hawker and Fréchet in 1990.[100] While the divergent method starts to build from the core molecule, the convergent protocol starts with the synthesis of the individual dendrons, via a similar protection and deprotection strategy, and then couples to a core molecule (Figure II.15), which results in smaller number of reactions.[97] When the desired generation is obtained, coupling to the deactivated core molecule is performed, which is a challenging final step due to steric hindrance. As a result, not all reactive groups on the core molecules will have coupled with dendrons. While an extra purification step will be necessary, separation is facilitated by the large differences in molar mass between the desired products and side products.

II.3.2.2 Hyperbranched polymers

The synthesis of HPs is more straightforward because of the one-step polymerization process, which does not require any activation and deactivation steps.[101] The polymerization process could be chain growth (ring-opening polymerization[102,103], free radical polymerization[104]) or step growth polymerization (polycondensation[105,106]) of AB_x monomers. Different subcategories could be distinguished if based on the nature of these AB_x monomers (Figure II.16).[96] The single-monomer method (SMM) uses only one type of AB_x monomers.[107,108] On the other hand, the double-monomer method uses A_2 and

B_3 type monomers.[109,110] The third method, couple-monomer method (CMM), combines the advantages of SMM and DMM by using A-A' and B'-B_2 monomers where A' and B' are more reactive.[111] Three or more different monomers are used in the multi-component method (MCM).[112,113] By varying the reactivity of the functional groups in the starting AB_x monomer, the DB value can increase, whereby the HPs behave more like dendrimers.

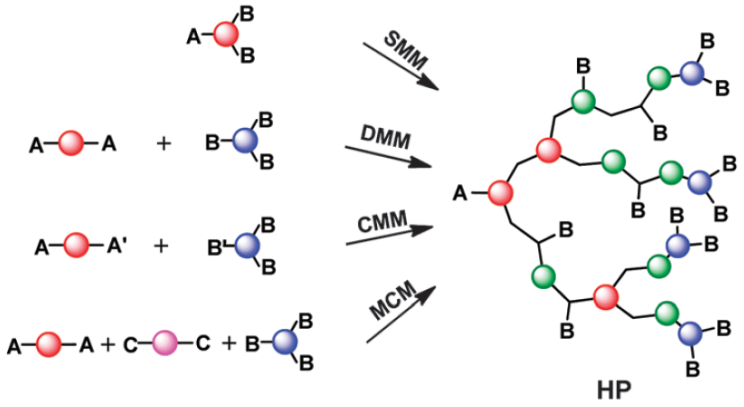


Figure II.16: Four types of synthesis methodologies for preparing HPs.[96]

II.3.3 Applications

Since the invention of dendrimers in 1978, research evolved extremely for different applications like medicine, catalysis, coatings,... Nowadays, only one commercial application is available, namely a pharmaceutical anti-HIV-agent VivaGel®.[114]

In the biomedical sector, where especially small scale applications are applied, dendrimers are more frequently applied than HPs because these meet the stricter requirements. These so called high-end applications could be drug delivery, catalysis and tissue engineering.[90] On the other hand, for large scale applications, HPs are the industrial standard because these are easier to manufacture and thus more cost-effective. This makes them very attractive as base for coatings.[115] Perstorp commercialize the first HP (Boltorn®) used for coatings.[101] A few years later, DSM introduced Hybrane® as another example of such an industrial standard, which is applied in paper coatings and fibers.[106]

Furthermore, research proved that HPs could be useful as polymer rheology control agents. In 1992, Kim *et al.* observed a drastic decrease in the melt viscosity of a polystyrene (PS) blend after addition of a minor amount of a HP. Moreover, the thermal stability

was not changed.[116] In 2000, Mulkern *et al.* showed that Boltorn® induced a decrease in the blend viscosity of PS and is therefore an excellent processing additive, because during processing, the HP behaves as lubricant, while in the final formation of the blend as toughening agent.[117]

Chapter III

Results and Discussion

III.1 Introduction

As mentioned in the introduction, the goal of this project is the exploration of the fast reaction of TAD-containing compounds with the focus on renewability and sustainability. Self-condensation of TAD-ene monomers towards linear and (hyper)branched polymers is investigated. As sustainability is a focus point of this manuscript, renewable starting materials are used whenever possible. Furthermore, the reactions are performed, where possible, via fast one-pot reaction mechanisms.

In order to obtain sustainable linear and (hyper)branched polymer in a fast manner, this project can be divided in two distinct chapters. The first chapter will discuss a sustainable synthesis route towards urazoles, while the second chapter focuses on the synthesis of linear and (hyper)branched polymers in which case the monomers undergo an intermolecular reaction.

III.2 Synthesis of sustainable urazole compounds

III.2.1 Introduction

As already explained in II.2.2.1, Cookson's original synthesis route in 1971 starts from different isocyanates to obtain the corresponding urazoles.[8] However, isocyanates are not only toxic but also have limited structural variety. To obtain more structural variety, carboxylic acids were proposed by Shimada *et al.* in 1990, in which case the corresponding isocyanate

is formed *in situ* via a Curtius rearrangement[53] with the aid of DPPA, which avoids the isolation and purification of the hazardous intermediates.[12] The main disadvantage of this reaction pathway is the toxicity and price of DPPA. Therefore, another effort to improve the sustainability of urazole compounds proposed the use of amines as starting materials. The two reaction pathways suggested by Mallakpour[9] and Breton[10] in 2007 and 2014, respectively, start from amines and make use of toxic and corrosive chloroformates as one of the starting compounds. Furthermore, in the Breton-synthesis, the amine is added in excess during the semicarbazide synthesis, inducing an extra purification step before the cyclization can be performed. This still limits the sustainability of urazole synthesis and therefore, the aim of this first chapter is to improve the sustainability of urazole synthesis starting from amines.

In this project, two different pathways are proposed, which are fully optimized alternatives, in terms of sustainability and efficiency, of the synthesis routes suggested by Mallakpour and Breton. The first method is thus based on the synthesis of an activated carbamate, which further reacts with ethyl carbazate (EC) towards a semicarbazide. In the second method, the semicarbazide is immediately obtained via reaction between a reactive intermediate and the amine. In both cases, a cyclization results in the urazole. These routes avoid the use of chloroformates, as diphenylcarbonate (DPC) was used in both reaction pathways.

In industry, DPC has recently draw a lot of attention in polycarbonate synthesis, because it is a more sustainable alternative than phosgene.[118] In the past decades, the synthesis of DPC has been performed via a few environmentally friendly processes, which all avoid the use of phosgene. A first method is the oxidative carbonylation of methanol with the aid of a catalyst (Figure III.1a), which can further react towards DPC via a transesterification with phenol (Figure III.1b).[119] A direct oxidative carbonylation of phenol is another often used methodology (Figure III.1c).[120] These synthesis routes show the highly added value of the synthesis route developed in this manuscript, as the released phenol (*vide infra*) can be recycled for the synthesis of DPC.

To meet the 12 principles of Green Chemistry of Anastas as much as possible (II.1.3), the sustainability of the synthesis routes was further improved by avoiding the use of isocyanates. Moreover, equimolar amounts are applied and solvents and purification steps are avoided where possible.

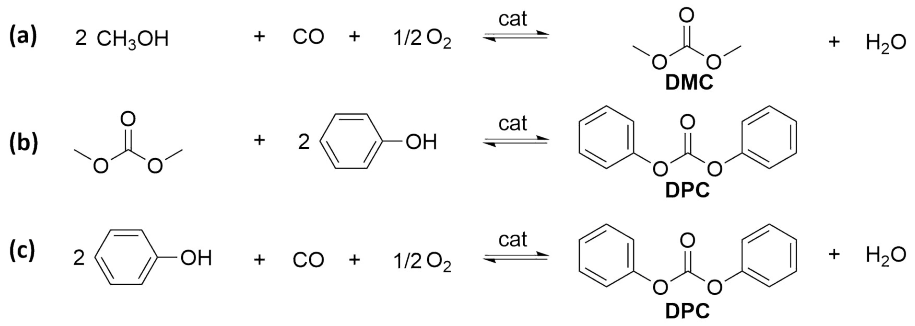


Figure III.1: (a) Oxidative carbonylation of methanol, (b) transesterification of DMC with phenol and (c) direct oxidative carbonylation of phenol towards DPC.

III.2.2 Synthesis route A - Via an activated carbamate

III.2.2.1 Synthesis via diphenylcarbonate

The first method is the more sustainable alternative of the method of Mallakpour in 2007 (Figure II.8a). The chloroformate was replaced by DPC, which reacts with an amine via an addition-elimination reaction step. The resulting activated carbamate is converted in a semicarbazide via reaction with EC at elevated temperature. In the final step of this one-pot reaction, the urazole is obtained via a thermal cyclization. All steps will be explained in detail in the following paragraphs (Figure III.2).

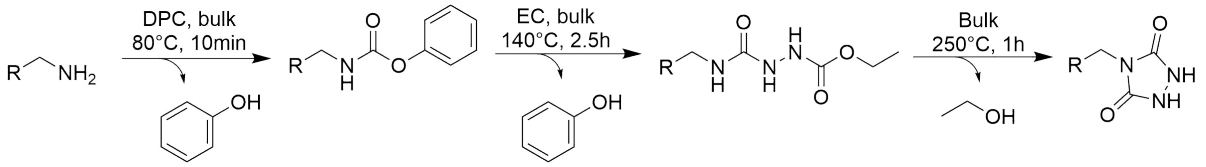


Figure III.2: The urazole is obtained in a one-pot reaction via the formation of an activated carbamate, which further reacts towards the corresponding semicarbazide and finally the product is obtained via a thermal cyclization.

In order to avoid the use of solvents, the first reaction step was performed in bulk. Therefore, a reaction temperature of 80 °C was applied, as this is the melting temperature of DPC. The reaction was followed via ^{1}H-NMR analysis and sample-taking proved that the reaction was already finished after five minutes. This shows that the reaction towards the activated carbamate was quasi instantaneous. However, for optimal mixing, a reaction time of 10 minutes was taken.

Although the first reaction step is fast and high-yielding, a minimal amount of side product could be observed in NMR, even when an equimolar ratio of amine and DPC was applied.

Both NMR and LC-MS analysis proved that a urea side product (5-10 %) was formed because of double amine addition to the DPC (Figure III.3). A systematic study showed that a twofold excess of amine resulted in only the urea product, while no urea side product could be observed upon addition of 2 equivalents of DPC. It thus seems interesting to apply an excess of DPC. However, intermediate purification would then be necessary to remove this excess, while the urea side product is automatically removed in the thermal cyclization step afterwards. Small amounts of urea were thus not cumbersome and only affected the yield. To maintain the one-pot process, purification was avoided and equimolar conditions were thus further used.

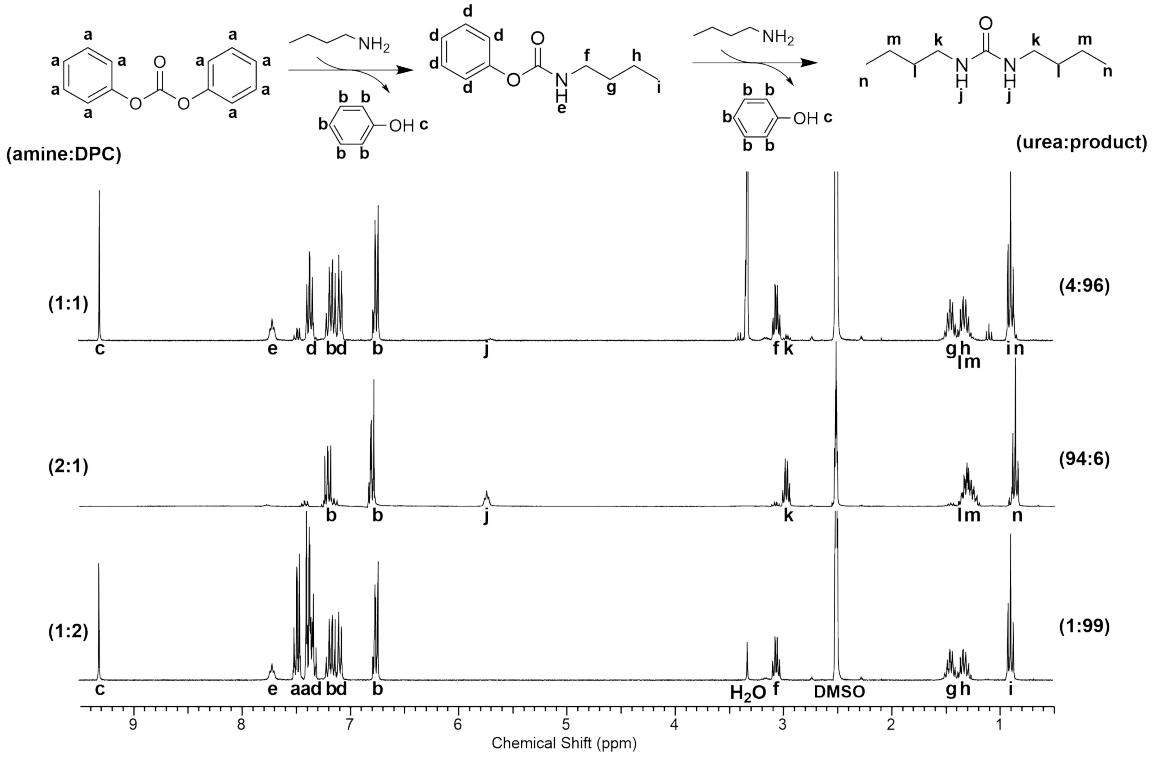


Figure III.3: A systematic NMR study showed that the urea side product is the main product when an excess of amine is used, while only the carbamate is formed upon addition of 2 equivalents of DPC.

The second step of the one-pot process included the addition of 1 equivalent of EC and an increase in temperature to 140 °C, which resulted in the formation of the corresponding semicarbazide and one equivalent of phenol. The kinetics of this reaction were tested, by taking an NMR-sample every 30 minutes. The conversion was calculated by comparing the NH-proton of the carbamate at 7.7 ppm with an NH-proton of the semicarbazide at 7.6 ppm. In the first 90 minutes, a linear increase was observed towards a conversion of 62 % and after 150 minutes, the reaction slowed down around a conversion of 80 % (Figure III.4).

Lower temperatures were also tested. However, a reaction temperature of 120 °C already required an overnight reaction. Therefore, a temperature of 140 °C was selected, which gave an optimal balance between reaction time and energy consumption. As the third step included an increase in temperature and thus a further increase in reaction rate, the reaction time of the second step was kept at 2h30. The urea side product that was formed in the first reaction step was unreactive towards the EC and remained unchanged in the reaction mixture.

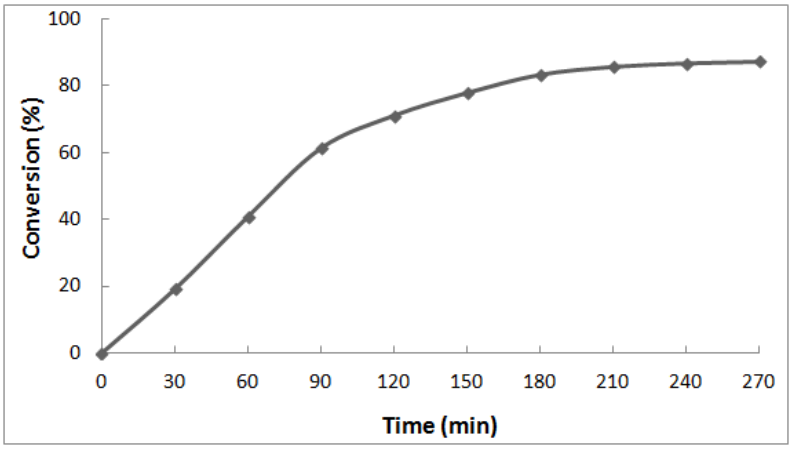


Figure III.4: Kinetic analysis of the formation of benzyl semicarbazide in the second step.

The third and final step of this one-pot procedure included the cyclization of the semicarbazide to obtain the corresponding urazole. Paquette *et al.* proposed a thermal cyclization at 250 °C for 30 minutes, which resulted in good yields.[121] In this case, reaction was also performed at 250 °C and a gentle nitrogen flow was applied to remove the formed ethanol and the phenol that was produced in the first two reaction steps, which has a boiling point of 182 °C. The cyclization was also tested at lower temperatures, in a range of 200 °C to 240 °C. It was shown that the cyclization was also initiated at 220 °C, but in this case, 250 °C was maintained to be sure that all the phenol was removed and the reaction was completely finished. In industrial processes, the phenol could easily be recuperated and regenerated towards DPC.

Again, the kinetics were tested by taking an NMR sample after every 30 minutes, but already after 30 minutes, the semicarbazide was completely converted into the corresponding urazole. Besides, the urea side product was completely removed from the reaction mixture. To make sure all the phenol was removed from the reaction mixture, the reaction was kept at 250 °C for 1 h in our procedure.

As can be seen in Table III.1, this methodology was applied to a wide range of amines with different R-groups. Both aliphatic, aromatic and bifunctional amines were tested. High yields were obtained when no competitive functionalities were present, for example when butyl-, benzyl- and cyclohexanemethylamine were applied, with yields of 86 %, 87 % and 86 % respectively. The ether-function in tetrahydrofurfurylamine proved to be resistant towards the harsh conditions of the last reaction step, as were also the mono- and disubstituted double bonds in allylamine and oleylamine. It should however be noted that in these cases a sufficient nitrogen flush is needed, to avoid side reactions with oxygen. Furthermore, it was observed that the yield was also determined by the volatility of the investigated amine. For example, the urazole derived from allylamine had a yield of 89 %, while the heavier oleylamine had a higher yield of 96 %. This can be explained by the volatility of the compounds under nitrogen flow at 250 °C.

It should also be noted that this methodology experienced difficulties when amines with competitive functionalities were applied like an alcohol or a second amine functionality (see bottom of Table III.1). This challenge and the characterization of the compounds will be explained in detail in the following paragraphs.

Table III.1: Overview of the used amines to form the corresponding urazole and their yields. n.s.: not successful.

R-NH_2	**Yield**
Butylamine	86 %
Octylamine	96 %
Benzylamine	87 %
Tetrahydrofurfurylamine	87 %
Oleylamine	96 %
Allylamine	89 %
Cyclohexaanmethylamine	93 %
3-amino-1-propanol	n.s.
Ethylene diamine	n.s.
Aniline	n.s.

Aniline

PhTAD is a well-known TAD compound and it is thus interesting to investigate its synthesis via the above described, more sustainable synthesis route with the use of aniline. First, the methodology described above was applied, but difficulties arose in the first step, resulting from the lower nucleophilicity of aniline compared to the other amines. Therefore, another method was searched to obtain the activated carbamate and found in the work of Harada *et al.*[122] They obtained the activated carbamate with the use of isobutyric acid as catalyst and 1.2 equivalents of aniline. In this case, longer reaction times (4 h) were needed to drive the reaction to completion. The carbamate was obtained but isobutyric acid and the excess of aniline were still present in the reaction mixture. To remove this catalyst, an extraction was performed with a 4M KOH solution. Although the catalyst could be removed from the reaction mixture, the excess of aniline was still present in the mixture. When the second reaction step was performed directly after the extraction, NMR analysis proved that side products were formed during the reaction. Column chromatography would thus be needed to remove the residual aniline from the mixture.

Therefore, an adapted version of Harada's recipe was performed, in which equimolar amounts of aniline and DPC were applied. However, no full conversion could be obtained after 24 hours, so residual aniline was still present. Column chromatography might offer a solution, but as avoidance of solvent was a main goal of this manuscript and phenyl urazole is one of the only commercially available urazoles, this synthesis was not continued.

3-amino-1-propanol

Another idea was to incorporate an alcohol functionality in a TAD compound. Therefore, 3-amino-1-propanol was used as starting material. In the first step, equimolar amounts of DPC and 3-amino-1-propanol were used. It was expected that the carbamate would be the major formed product because the amine is a better nucleophile than the alcohol. But in this case, the reaction with the amine and with the alcohol towards the carbonate were both so fast, that a mixture of carbamates and carbonates was obtained, which was shown in the ^{1}H-NMR spectrum. LC-MS proved that a product of 195.22 g/mol was formed, but this could be both the wanted carbamate (1) or the carbonate (2), where the hydroxyl reacted to the DPC (Figure III.5). Besides, the urea (3) was formed, which has

a molecular weight of 176.22 g/mol, although this could also be carbonate (4), where the alcohol functionalities reacted or a mixture of both. Furthermore, also products with a molecular weight of 296.32 and 315.33 g/mol were formed, which could be respectively (5) and (6). The reaction mixture thus contained a lot of side products and purification was too complicated. The reaction was stopped after the first step because a sustainable synthesis with 3-amino-1-propanol was not possible via this methodology.

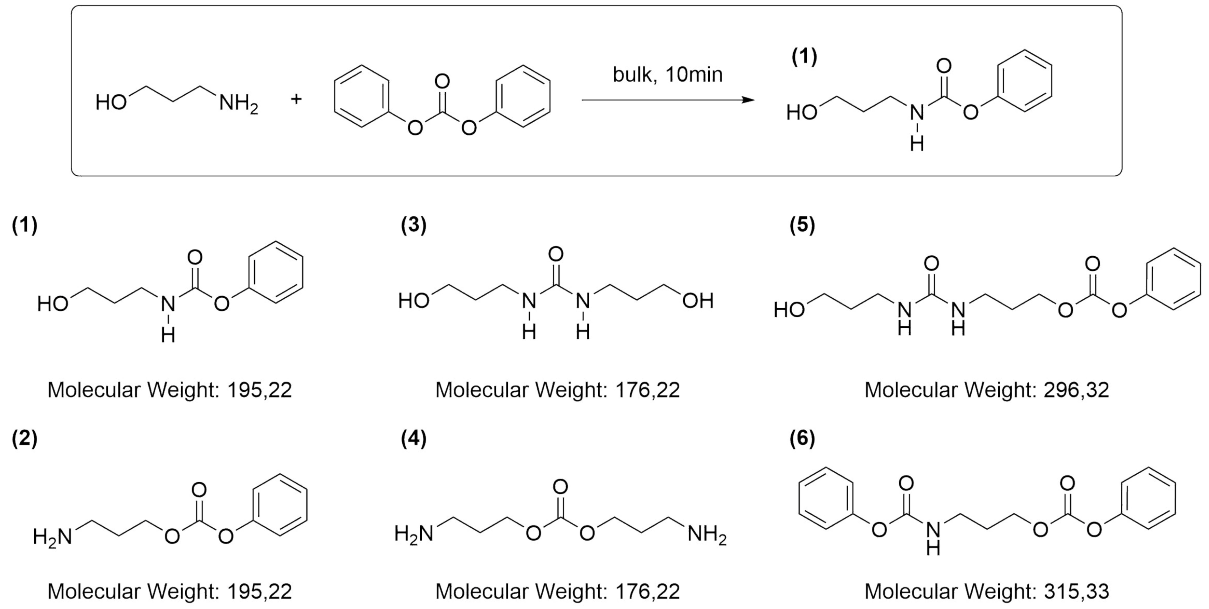


Figure III.5: Product and side products of the first reaction step with 3-amino-1-propanol.

Ethylenediamine

Ethylenediamine was used as starting compound, with the aim to obtain a bis-TAD structure, which could be used as a potential crosslinker. In this case, two equivalents of DPC were added to one equivalent of ethylenediamine. The first reaction step was performed at the usual reaction conditions of 80 °C in bulk for 10 minutes, but next to the expected carbamate (1), LC-MS proved that also other side products were formed (Figure III.6). Side product (2) was formed when only one amine reacted with DPC. Next to the above mentioned urea side product (3), the urea could further react with DPC (4). All those side products were formed because both amine functionalities of ethylenediamine are equally reactive towards the bifunctional DPC and a large local excess of amines can be present in the reaction mixture. With all those side products in the reaction mixture, purification would be very difficult. Therefore, further research to obtain a bis-TAD structure from ethylenediamine via this methodology was stopped here.

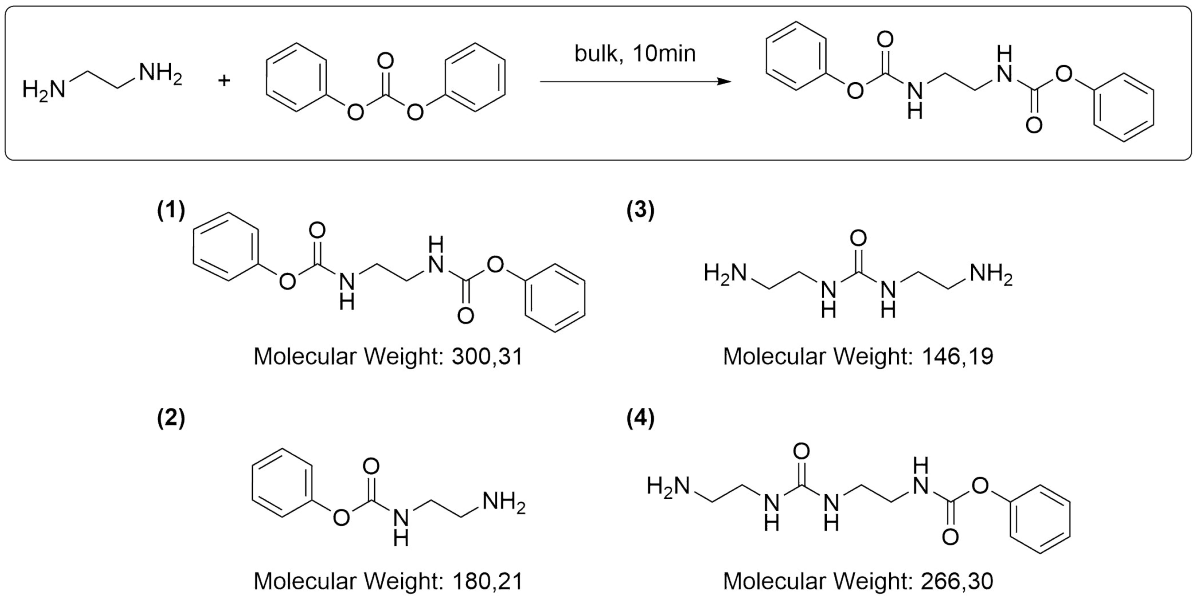


Figure III.6: Product and side products of the first reaction step with ethylenediamine and DPC.

Characterization of all obtained urazoles was performed by ^{1}H-NMR, ^{13}C-NMR, IR and LC-MS. In Figure III.7, the complete ^{1}H-NMR analysis of the synthesis towards butyl urazole is shown.

In the first step, phenol was formed, which is still visible in the spectrum at 6.7-7.2 ppm and at 9.3 ppm. The carbamate functionality can be seen at 7.7 ppm. In this case, 5 % of the urea side product was obtained, resulting in a triplet at 5.7 ppm. Furthermore, all the peaks of DPC have disappeared. In the second step, the carbamate NH-peak at 7.7 ppm disappeared, while the characteristic peaks of the semicarbazide appeared at 6.3, 7.6 and 8.7 ppm. The urea side product is still present at 5.7 ppm. The integration of the peaks of phenol are doubled, as two equivalents are present after the first two steps. In the final step, the semicarbazide turned in the corresponding urazole, which was visible by removal of the characteristic peaks of the semicarbazide and the appearance of the acidic protons of the urazole at 9.9 ppm. As can be seen from the spectrum, both the residual phenol and the urea side product were removed by the high temperature treatment and the nitrogen flow.

Next to ^{1}H-NMR, ^{13}C-NMR was used to check the purity of all formed urazoles. Figure III.8 shows the ^{13}C-NMR of butyl urazole, which demonstrates that the product was pure, as no traces of urea or phenol can be observed. Furthermore, all resulting urazoles were

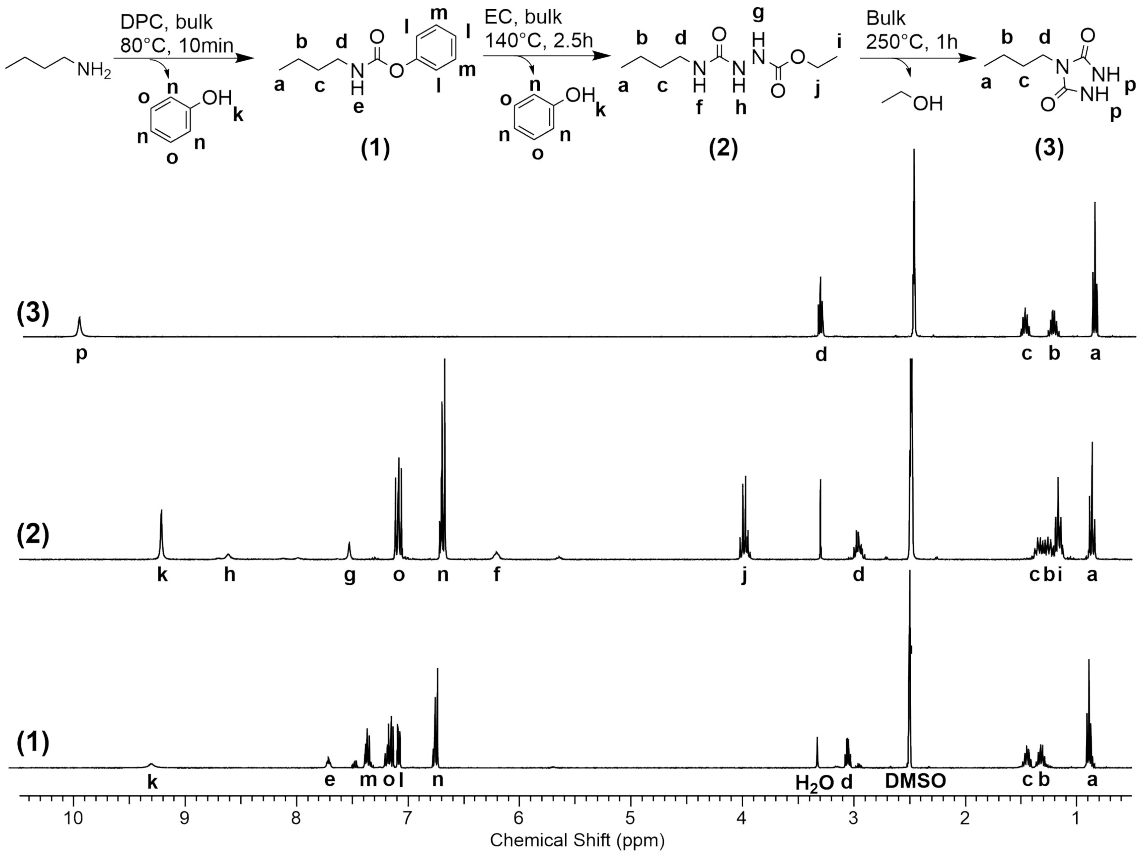


Figure III.7: ^{1}H-NMR spectrum of (1) butyl carbamate, (2) butyl semicarbazide and (3) butyl urazole.

subjected to IR. In all spectra, the typical C=O stretches were visible around 1660 and 1760 cm^{-1}, as well as one broad absorption of N-H stretches around 3160 cm^{-1}. As the absorptions of the side groups were often located in the fingerprint area, these will not be discussed in detail.

III.2.2.2 Synthesis via dimethylcarbonate

The above described synthesis already significantly improved the synthesis as described by Mallakpour *et al.* in 2007. However, the sustainability could be even more improved when dimethylcarbonate (DMC) could be applied instead of DPC. This would avoid the transesterification from DMC towards DPC, which is an energy-inefficient process and it would avoid the handling of phenol.

Therefore, the above reaction route was tested with DMC. The first reaction step was performed in bulk at 70 °C, as the boiling point of DMC is 80 °C. It was however shown that this reaction step needed 24 hours to reach complete conversion, compared to 10

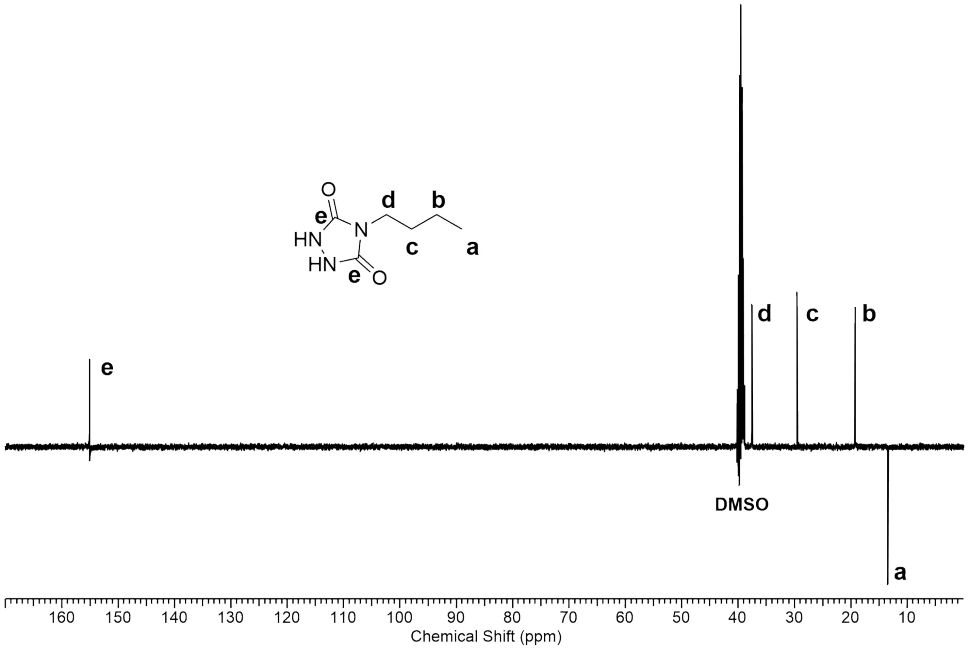


Figure III.8: ^{13}C-NMR analysis of butyl urazole.

minutes in case of DPC. This should be taken into account when energy consumption needs to be limited. Furthermore, the second step showed to be even more challenging, as, up until now, no reaction at all could be observed, at a variety of conditions, including an increase in temperature up to 160 °C, the addition of catalysts such as TBD and DBU or increasing reaction times up to 48 hours. The reason for this is the reduced reactivity of the methyl carbamate, as the phenoxy-group of DPC is a better leaving group than the methoxy-group of DMC.

Within the limited time span of this project, no solution for this reaction could be found. However, in view of sustainability, it would definitely be interesting to further investigate whether this reaction is possible and under which circumstances.

III.2.3 Synthesis route B - Via an activated intermediate

As the first synthesis route via the activated carbamate showed some problems when functional amines were used, a second synthesis route was investigated. This route enhances the synthesis as described by Breton *et al.*, who used an activated intermediate to obtain the semicarbazide in one step. The main disadvantages of this methodology were the use of 2.2 equivalents of amine and the use of solvents, both during the reaction and work-up afterwards. A more sustainable alternative is provided here.

Figure III.9 summarizes the second synthesis pathway, in which a semicarbazide is formed in the first step via an addition-elimination step of the amine to ethyl phenyl hydrazine-1,2-dicarboxylate (EPHD). As a second and final step, the semicarbazide is transformed towards a urazole via a thermal or basic cyclization.

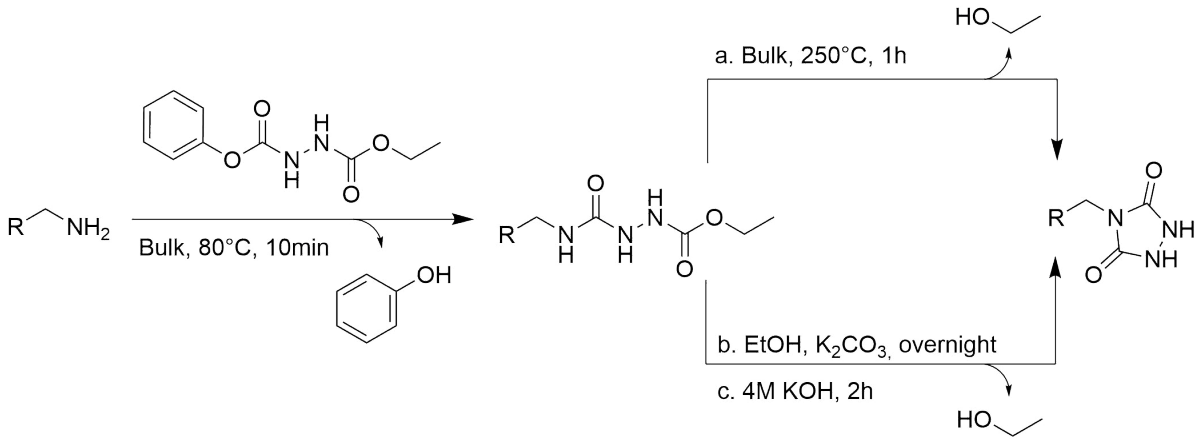


Figure III.9: The urazole is obtained in a one-pot reaction via the direct formation of the semicarbazide, which further reacts towards the urazole via a thermal or basic cyclization.

III.2.3.1 Synthesis of ethyl phenyl hydrazine dicarboxylate

As can be seen in Figure III.9, the activated intermediate EPHD is used in the first step to immediately obtain the semicarbazide via an addition-elimination reaction with an amine. The classical synthesis route to obtain EPHD, as applied by Breton *et al.*, makes use of phenyl chloroformate, which reacts with EC in the presence of DIPEA in DCM. However, as phenyl chloroformate is shown to be toxic and corrosive, a first improvement was the use of DPC instead of the more toxic chloroformate (Figure III.11).

Boger *et al.* already made a hydrazide via reaction between one equivalent tert-butyl carbazate and one equivalent bis-(2,4-dinitrophenyl)carbonate in EtOAc at RT for 2 hours.[123] The same principle was tried, but in order to obtain EPHD in a sustainable way, DPC and EC were used. The reaction was performed in EtOAc for 2 hours, but no reaction occurred, not even at a higher temperature of 60 °C and longer reaction times of 24 hours. The reaction was repeated with the same equimolar amounts but in bulk at 90 °C, which was more successful with a conversion of 73 % after 2 hours. Working in bulk was already a progress in comparison with the syntheses of Breton and Boger. To further improve the reaction conditions, two catalysts, TBD and DBU, were tested. An

NMR-sample was collected every 30 minutes and conversion calculated (Figure III.10a). In the first 30 minutes, the conversion increased the most in the case of DBU as catalyst, but after 40 minutes, the rate slowed down and ended after 2 hours with a lower conversion compared with the blank test and with TBD as catalyst. After 2 hours, the blank test had the highest conversion. As conclusion, the two catalysts did not offer a significant advantage in comparison to the blank test.

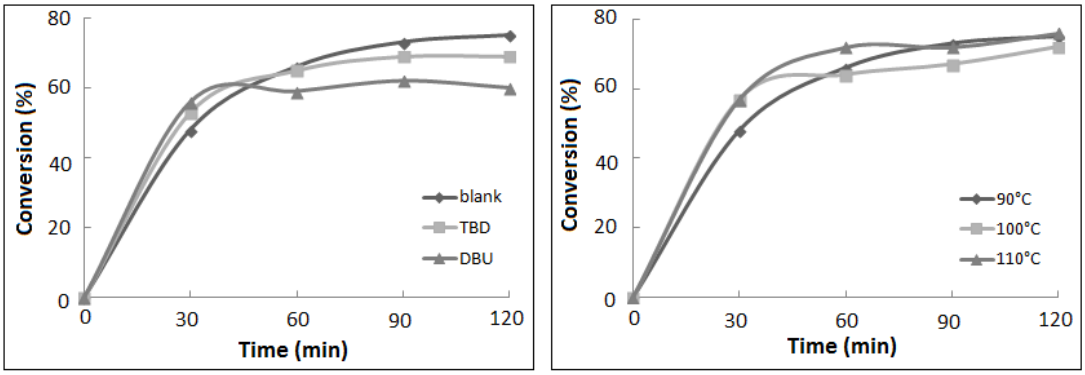


Figure III.10: Conversion of EC and DPC towards EPHD as a function of the reaction time with varying (a) catalysts and (b) reaction temperatures.

Afterwards, the effect of reaction temperature was investigated by increasing the reaction temperature to 100 °C and 110 °C (Figure III.10b). However, no significant improvement was observed upon temperature increase, so reaction was kept at 90 °C because this is more energy efficient. Furthermore, an increase in reaction time to overnight reaction was tested, which resulted in a conversion of 89 %. Although this is an increase of 14 %, it is not a lot in comparison with the extra energy needed, so other solutions were sought after. In a final test, a twofold excess of EC was used, which resulted in complete conversion after 1 hour at 80 °C. The excess of EC could easily be removed by precipitation in water and could in principle be recuperated for next reactions. The white precipitate was dried under vacuum at 40 °C overnight to remove water, which resulted in a yield of 76 %.

Figure III.11 summarizes the optimized reaction condition to obtain EPHD. The use of DPC and reaction in bulk makes this reaction more sustainable than already proposed reactions. Next to the reduced toxicity, an extra advantage of using DPC over chloroformates is that the produced phenol could be recycled in industrial processes.

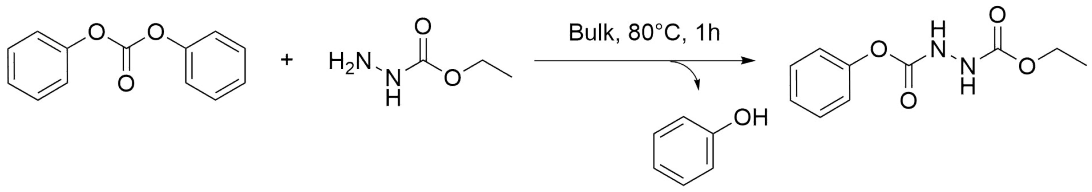


Figure III.11: Synthesis of EPHD via reaction between EC and DPC in bulk.

III.2.3.2 Synthesis of urazoles with EPHD

With the pure EPHD, Breton obtained the semicarbazide via a reaction between one equivalent EPHD and 2.2 equivalents of alkylamines in acetonitrile. Subsequently, the mixture was subjected to column chromatography for purification and the urazole was obtained via basic cyclization.

In our case, the addition-elimination step was performed in bulk at 80 °C, the melting temperature of EPHD, to obtain the semicarbazide. A kinetic analysis was executed by taking an NMR-sample every 5 minutes. After already 5 minutes, the NMR proved that the reaction had a conversion of 100 %, which demonstrated the fast reaction with the activated intermediate. In the next experiments, the reaction time was kept at 10 minutes to ensure complete reaction. Another advantage of this method was that no urea side product was formed. Therefore, a thermal cyclization was still possible, but not obliged, as a basic cyclization is also a possibility without the need for intermediate purification.

As mentioned before, the urazole was obtained by thermal or basic cyclization. Just as the first methodology, the thermal cyclization was performed at 250 °C for 1 h under a gentle nitrogen flow to remove the produced phenol. The basic cyclization was applied when thermal cyclization was no option because of the present functionalities. The basic cyclization is performed under milder reaction conditions but longer reaction times are required. The reaction occurred in EtOH and 5 equivalents of K_2CO_3 were added. If the synthesized urazole precipitates in water, the basic cyclization can also be performed in a 4M KOH solution.

As can be seen in Table III.2, this methodology was applied to the same amines as in the first methodology. Again, high yields were obtained when no competitive functionalities were present, for example when butyl-, benzyl- and cyclohexanemethylamine, with yields of 89 %, 85 % and 95 % respectively. Breton also synthesized semicarbazides starting

from butyl- and benzylamine with yields of 86 % and 76 % respectively, but with our methodology, higher yields were obtained in both cases for the overall reaction.

With this methodology, some urazoles were cyclized via a basic cyclization to avoid side products and this was the case for urazoles based on tetrahydrofurfurylamine, 3-amino-1-propanol and cysteamine.

Table III.2: Overview of the used amines to form the corresponding urazole with the second methodology and their yields. [a]: thermal cyclization, [b]: basic cyclization (EtOH, K_2CO_3), n.s.: not successful.

R-NH_2	**Yield**
Butylamine	89 % [a]
Octylamine	95 % [a]
Benzylamine	85 % [a]
Tetrahydrofurfurylamine	90 % [b]
Oleylamine	95 % [a]
Allylamine	84 % [a]
Cyclohexaanmethylamine	95 % [a]
3-amino-1-propanol	78 % [b]
Ethylene diamine	92 % [a]
Cysteamine	27 % [b]
Aniline	n.s.

As mentioned above, with the first methodology, difficulties were experienced upon urazole synthesis with aniline, 3-amino-1-propanol and ethylenediamine. The same amines were tested with this second methodology. Breton already showed that aniline was unreactive towards EPHD if the reaction was performed in acetonitrile at RT and reflux temperatures. Also in this case, aniline was unreactive towards EPHD in bulk at 80 °C for 10 minutes and even at longer reaction times of 24 hours (Figure III.12a). A phenyl urazole obtained with aniline as starting material was thus shown to be difficult to obtain via the above described methods.

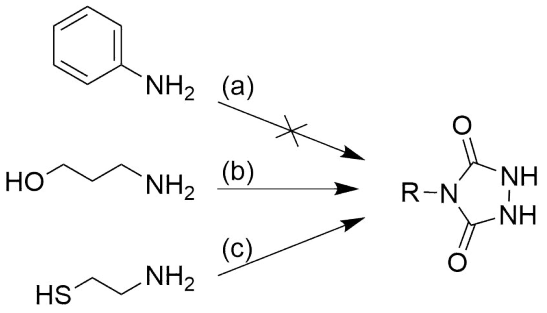


Figure III.12: (a) Attempted synthesis of phenyl urazole based on aniline and synthesis of urazoles based on (b) 3-amino-1-propanol and (c) cysteamine.

In contrast to the first methodology, the alcohol-functionalized urazole starting from 3-amino-1-propanol could be formed because of the use of the reactive intermediate (Figure III.12b). EPHD has a preference to react with the amine rather than the alcohol because the former is more nucleophilic. In EPHD, the phenoxy group is a much better leaving group than the ethoxy group and therefore, only one reaction takes place towards the dicarboxylate. It should be noted that the basic cyclization was applied to avoid side reactions at elevated temperatures. Finally, a yield of 78 % was obtained.

As the synthesis of an alcohol-functionalized urazole was no problem via this synthesis route, a urazole with a thiol end-group was envisioned. This might have interesting applications when TAD-chemistry and thiol-ene chemistry could be combined. To achieve this thio-urazole, cysteamine was used as a starting compound (Figure III.12c). Because the amine is a better nucleophile than the thiol group, only the wanted semicarbazide was obtained. In analogy with the hydroxy-urazole, a basic cyclization was applied, leading to a yield of 27 %. This yield could maybe be enhanced by prolonging the reaction time of the basic cyclization or by applying the stronger NaOEt as a base instead of K_2CO_3. Although the yield is low, this is the first time that a thiol-functionalised urazole could be synthesized. It should be noted that, in the case of 3-amino-1-propanol and cysteamine, oxidation towards the corresponding TAD compound should be performed *in situ* in order to avoid side reactions, namely oxidation of the alcohol and thiol (Figure II.11). Another option is to first use the thiol/alcohol in the envisioned reaction and only oxidize the TAD compound in a later stage.

Also a bis-urazole was obtained with ethylenediamine as starting compound. Because the phenoxy group was the best leaving group of the reactive intermediate, only one equivalent

of the excess of amines can react with EPHD and thus only the wanted bis-semicarbazide was formed. In this case, thermal treatment was applied as no side-reactions were expected, leading to a yield of 92 %.

Characterization of the urazoles was again performed by ^{1}H-NMR, ^{13}C-NMR, IR and LC-MS. In Figure III.13, the complete ^{1}H-NMR analysis of the synthesis towards oleyl urazole is shown. Phenol was formed in the first step, which is still visible in the spectrum in the aromatic region of 6.7-7.2 ppm. The peaks of EPHD disappeared and no urea side product was formed. The characteristic peaks of the semicarbazide itself appeared at 6.3, 6.6 and 8.7 ppm. In the cyclization step, the oleyl urazole was obtained via a thermal cyclization. All the phenol and ethanol were removed by the nitrogen flow. Because of the insolubility of oleyl urazole in deuterated DMSO, the spectrum was taken in deuterated chloroform. Therefore, the peaks of the semicarbazide and the acidic urazole protons are not visible. However, a clear shift of the α-CH_2 protons (f) from 2.9 ppm in the semicarbazide to 3.5 ppm in the urazole can be observed.

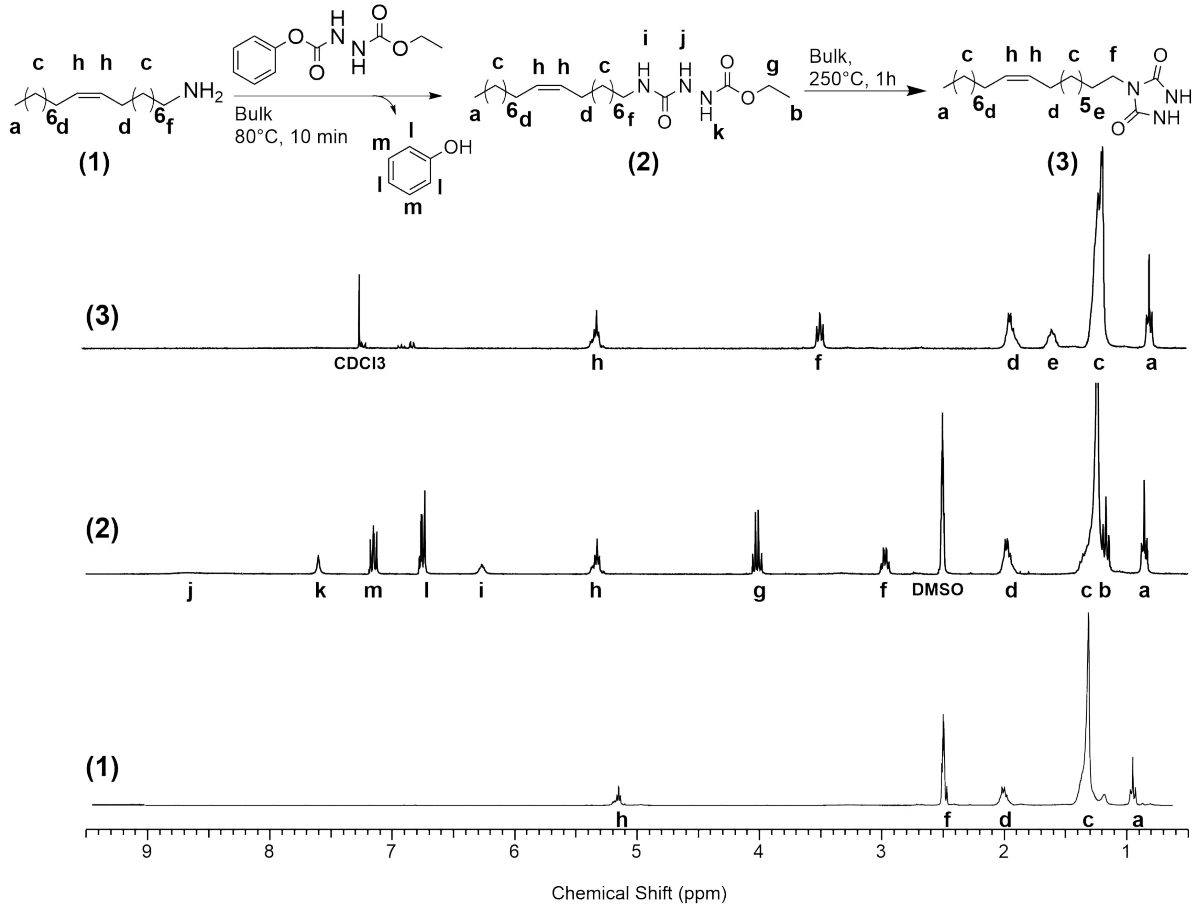


Figure III.13: ^{1}H-NMR analysis of (1) oleylamine, (2) oleyl semicarbazide and (3) oleyl urazole.

Furthermore, the purity of all urazoles was checked via ^{13}C-NMR. Figure III.14 shows the ^{13}C-NMR of oleyl urazole, which demonstrates that the product was pure, as no traces of phenol can be observed. Just like for the first methodology, again all urazoles were subjected to IR. The LC-MS results from the synthesized urazoles can be found in Appendix A.

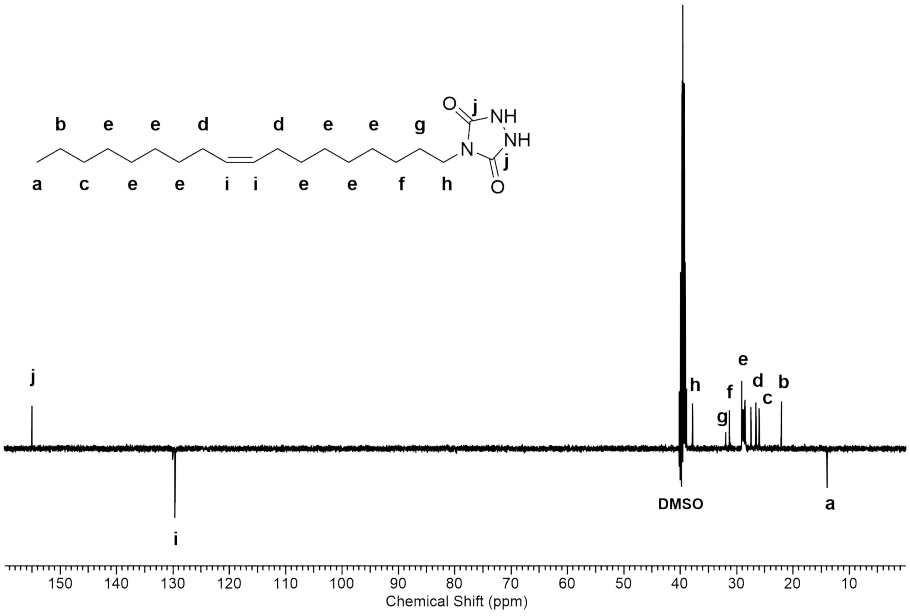


Figure III.14: ^{13}C-NMR analysis of oleyl urazole.

III.2.4 Conclusion

The synthesis towards sustainable urazoles was successful with the two routes and could be regarded as a breakthrough development for the synthesis of a library of TAD compounds. Depending on the starting product and desired incorporated functionalities, one synthesis route is preferred over the other. The urazoles with alkyl or related functionalities were perfectly obtained with high yields via the first method, while the second methodology allowed the introduction of more competitive groups such as alcohols and thiols. While the original synthesis routes of Mallakpour and Breton also result in high yields, the synthesis developed in this project are more sustainable, as chloroformates and solvents are avoided and equimolar amounts are applied. Furthermore, the one-pot process enhances the easiness of the syntheses and strongly reduces the reaction time, as the reactions are fast, quantitative and there is no need for intermediate purification.

III.3 Applications of sustainable urazoles in polymers

III.3.1 Introduction

As seen in II.2.4, a multitude of polymer applications have been arising, which are based on the exceptional TAD reactivity. A high interest in this compound is observed in the field of green chemistry, mainly because of its high reactivity at RT towards dienes and enes in a DA- or AE-reaction pathway, respectively. Unfortunately, the application of TAD compounds was, until now, limited by their low commercial availability and therefore had limited use in industrial context. Their lack of availability and their burdensome, harmful synthesis was overcome in the first chapter of this project by the straightforward synthesis of the corresponding urazoles.

In the second part of this project, TAD compounds were tested in polymer applications. The modifications of linear polydienes was already investigated by Butler and co-workers in 1979, but in our research, the first envisaged application was to form linear polymers with TAD-adducts in the polymer backbone. The presence of such adducts with strong hydrogen bonding effect in the backbone could result in particular physical properties. In order to optimize the sustainability of the polymers, renewable starting compounds were selected and the reactions were, where possible, performed via fast one-pot reaction mechanisms.

Furthermore, the use of TAD compounds was until now never investigated in hyperbranched polymers (HPs). Functional AB_2-monomers including TAD moieties were therefore investigated, which could further react towards HPs via an easy one-pot process. The selected (di)enes were also bio-sourced materials, to further increase the sustainability.

III.3.2 Linear polymers

The idea to obtain linear polymers was based on the fact that TAD compounds are highly reactive towards unsaturations. It should thus be straightforward to obtain a linear polymer if a TAD compound undergoes an intermolecular reaction with a double bond located in the R-group of the TAD compound. The color change after oxidation could be employed to follow the reaction from the TAD compound towards the polymer.

As a linear polymer was envisioned, an AB-monomer was searched for. The TAD-moiety represented the first functionality and to obtain AB-monomers, one double bond or diene should be present in the TAD side chain. As renewable starting compounds were envisioned, the already synthesized oleyl urazole met the requirements (Figure III.13). Another option could be the synthesized allyl urazole. However, as explained in II.2.3, TAD reacts faster with more substituted double bonds, therefore, oleyl urazole was selected for this purpose.

III.3.2.1 Oleylamine

In 2014, Türünç *et al.* already showed that oleyl alcohol reacts with PhTAD via an AE-reaction.[88] As the AE-mechanism dictates, two isomers were obtained and the double bond was not consumed but shifted to the next position. To obtain a linear polymer, oleyl urazole should be synthesized starting from oleylamine. This synthesis was already described in section III.2 via both route A and B, with yields of 96 % and 95 %, respectively.

To induce the polymerization, the unsaturated urazole was oxidized towards the corresponding TAD compound. In a first trial, N-bromosuccinimide (NBS) was used as oxidant in dry THF and pyridine. The idea to choose this oxidation method was that, after polymerization, the polymer would precipitate and all other components would stay in solution. However, after oxidation, pyridine salts precipitated, while the polymer and NBS were still soluble. In order to remove the NBS that is present, precipitation in cold methanol was tried, however, the polar acidic protons in the polymer prevented the precipitation. In a second attempt to precipitate the polymer, hexane was applied, but also NBS precipitated. In order to avoid this purification challenge, another oxidation method was searched.

Because the polymer, made during the first attempt with NBS, was soluble in dichloromethane (DCM), a heterogeneous oxidation with DABCO-Br in DCM was tried (Figure III.15c). The main advantage of this heterogeneous oxidation is that, after oxidation, the oxidant can be filtered off easily, while the polymer was still soluble in DCM. After filtration, the red reaction mixture was further stirred overnight and the red color became yellow. Because of the AE-reaction that occurred, the oleyl TAD polymerized towards a linear polymer, which was a viscous oil (Figure III.15d).

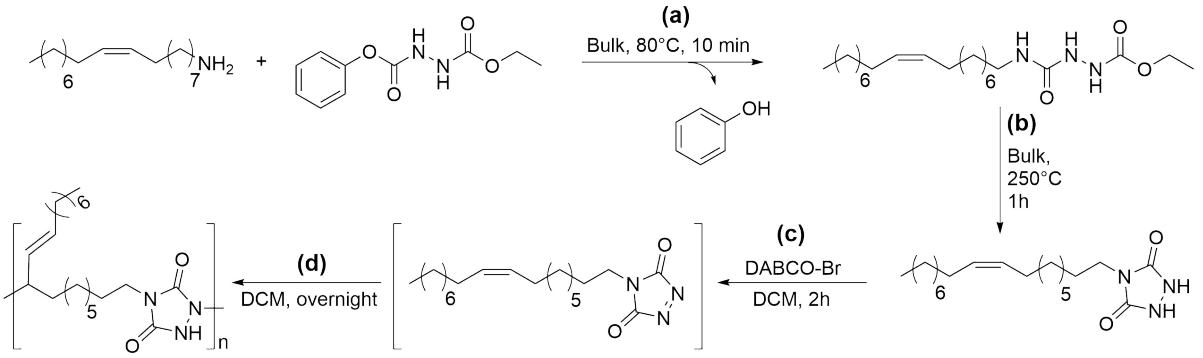


Figure III.15: (a) Semicarbazide formation between oleylamine and EPHD according to step 1 of route B and (b) thermal cyclization towards oleyl urazole. (c) Oxidation of the urazole to oleyl TAD with DABCO-Br results in (d) direct polymerization of the TAD compound to a linear polymer.

The next step was, of course, the characterization of the synthesized polymer.

The molecular weight was determined via SEC, as NMR did not allow proper molecular weight determination. SEC in THF showed a molecular weight of 3400 g/mol and a dispersity of 1.4 (Figure III.16). This is a relative measurement on a system that is calibrated with polystyrene (PS). Because of the long side chains that are present in the polymer and the large difference in polarity between the long aliphatic chain and the polar urazole-moiety (Figure III.15), the standard does not come close to the structure of the investigated polymer. This will of course influence the result of the SEC and the interpretation of these results.

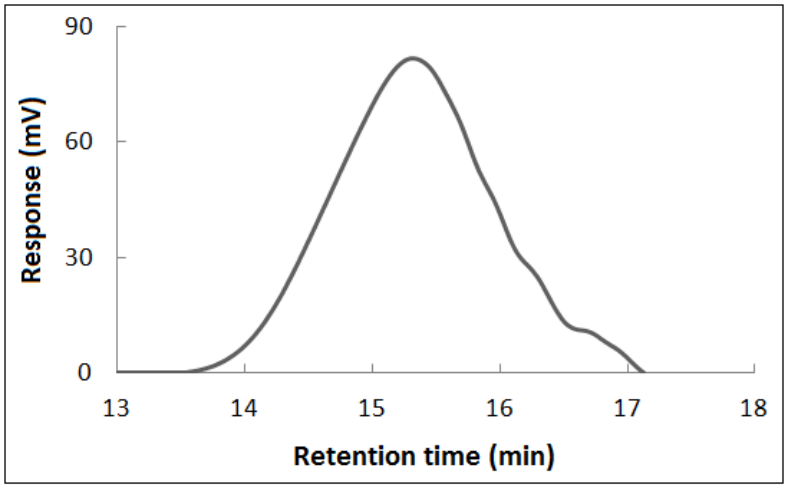


Figure III.16: THF-SEC of the linear polymer started from oleyl urazole.

Thermal analysis of the polymer showed that the polymer degrades starting from 205 °C (Figure III.17). When the degradation temperature was known, DSC could be performed,

mainly to obtain the T_g, which was finally -8 °C. Although this is not a high T_g, this was not expected, because of the high degree of flexibility in the polymer backbone. No crystallinity could be observed, which might be because of the long side chains that are present, avoiding the alignment of the polymer backbones.

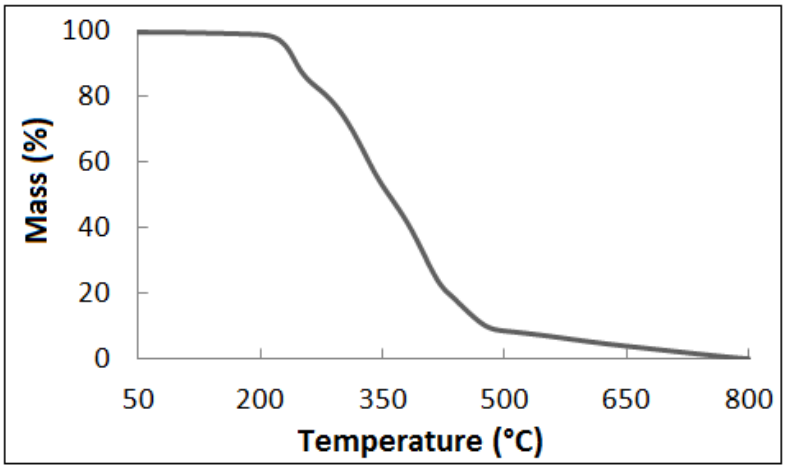


Figure III.17: Thermal gravimetric analysis (TGA) of the linear polymer of oleyl urazole performed in the range of 30 °C to 800 °C with 10 °C/min under nitrogen atmosphere.

It can thus be concluded that it is possible to make an AB-monomer from oleylamine and that this can further be polymerized in an easy process. It should however also be noted that the polymerization process is rather slow, as it takes overnight stirring. In order to avoid this long polymerization time, another monomer was looked for.

III.3.2.2 Citronellol

While oleyl urazole contains a di-substituted double bond, it is known that more substituted double bonds show faster reaction kinetics in the AE-reaction with TAD (see II.2.3). Therefore, the terpene citronellol with its tri-substituted double bond could be an interesting starting product. However, an amine functionality, which can be converted in the corresponding urazole, is absent. In the next paragraph, the reactivity of PhTAD towards citronellol was tested as model reaction. Furthermore, two reaction routes that exploit the unique reactivity of citronellol toward TAD compounds for the formation of linear polymers were investigated.

Reaction of PhTAD with citronellol First, the reactivity of PhTAD towards citronellol was tested. The reaction was performed in a solvent in which both starting materials would dissolve. An equimolar amount of PhTAD in DCM was added to a solution of citronellol in DCM (Figure III.18). After 1 minute stirring at RT, the red solution already turned yellow. This change in color is one the advantages of TAD chemistry as it means that the TAD compound is completely consumed towards the TAD-ene adduct. Furthermore, it can be noted that this reaction is a lot faster than the reaction of PhTAD with oleyl alcohol.[88] In Figure III.18, the ^{1}H-NMR analysis is shown, which proved that a quantitative AE-reaction occurred at the double bond because a peak at 4.42 ppm appears, which represents the proton next to the urazole-moiety. Furthermore, the $CH_{3,b}$ peak at 1.57 ppm is completely removed and an extra peak appears at 5 ppm with an integration of two, which represents the terminal $CH_{2,j}$. Most importantly, the acidic proton at 10.9 ppm indicates that the TAD compound turned into the corresponding adduct.

To conclude, an AE-reaction occurred between citronellol and a TAD compound. The double bond was shifted towards a terminal position.

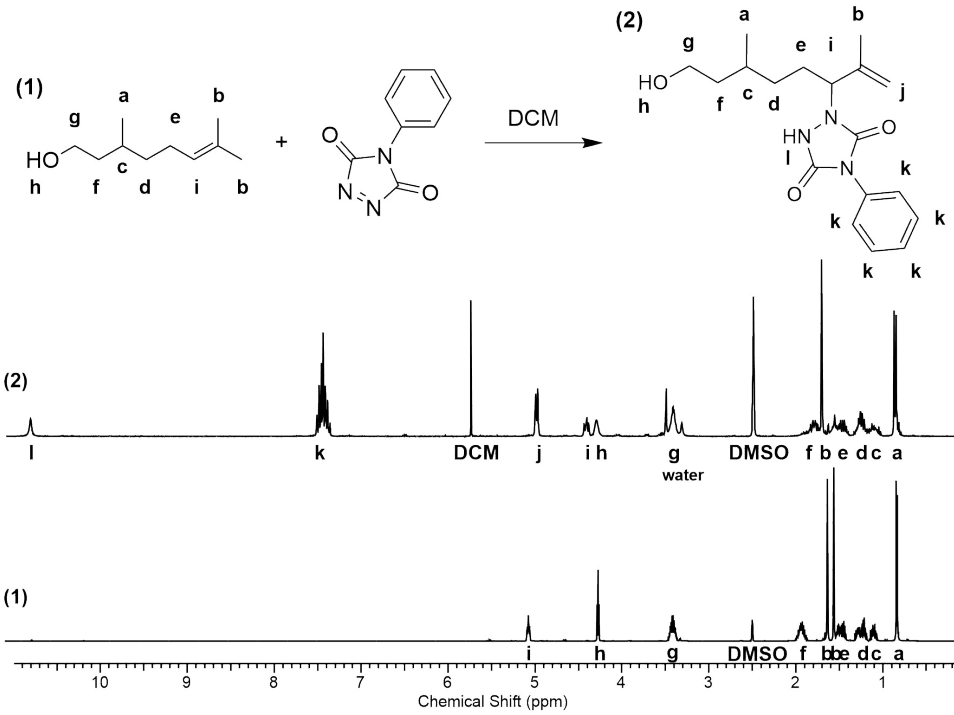


Figure III.18: ^{1}H-NMR analysis of (1) citronellol and (2) the AE-adduct of citronellol and PhTAD.

Linear polymers via esterification of citronellol and a carboxylic acid TAD

The first idea to obtain linear polymers started from citronellol and the functionalities that are present in this bio-sourced molecule. The tri-substituted double bond offers possibilities for functionalization with TAD, while the alcohol might be interesting for esterification reactions. Therefore, the idea arose to synthesize a urazole compound with a carboxylic acid functionality, which could then be used in combination with citronellol to obtain linear polymers (Figure III.19). To obtain a urazole with a carboxylic end group, the amino acid 6-aminocaproic acid was selected.

In a first reaction pathway, the TAD compound reacts to citronellol via an AE-reaction and after an esterification reaction, the linear polymer would be obtained. A second considered option was that first an esterification reaction between citronellol and the caproic acid urazole could occur and after oxidation of the urazole, the polymer could be formed via an AE-reaction.

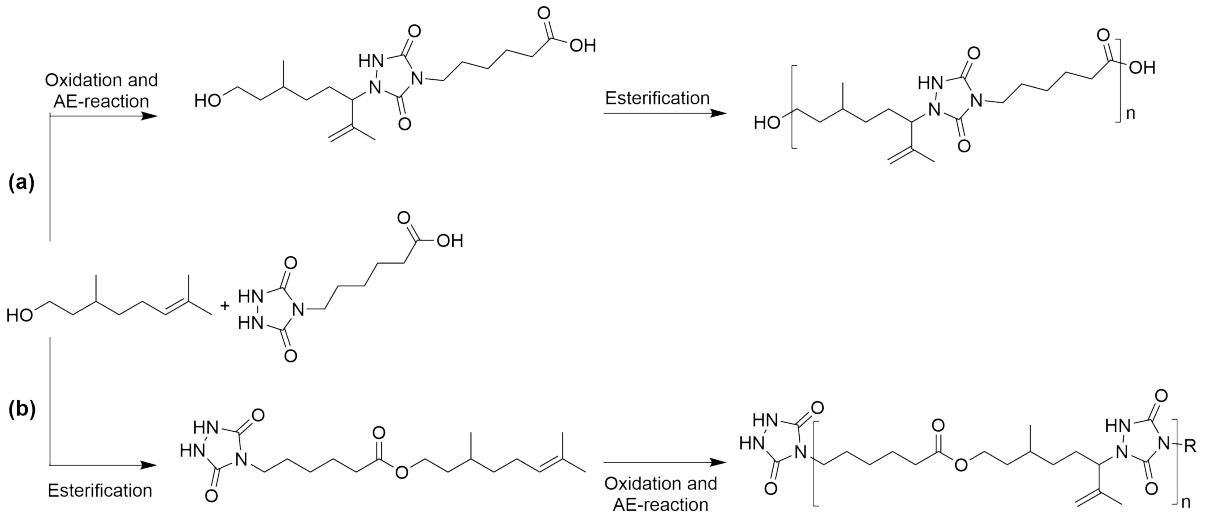


Figure III.19: Route towards linear polymers starting from citronellol and 6-aminocaproic acid urazole via (a) oxidation and AE-reaction, followed by esterification or (b) vice versa.

Synthesis of caproic acid urazole

In a first phase towards the caproic acid urazole, route A was tried (see III.2.2). To obtain the carbamate, the amino acid 6-aminocaproic acid was added to DPC at the conventional 80 °C in bulk. Because 6-aminocaproic acid has a melting point of 208 °C, a pressure tube was used but the amino acid was not melting and no reaction occurred. When the temperature was increased towards 110 °C, the activated carbamate was formed. However,

when the temperature was further increased for the second step, namely 140 °C, and EC was added, the ^{1}H-NMR analysis showed a lot of impurities, which could be the result of a decarboxylation of the carboxylic acid.

Therefore, in a next experiment, the amino acid was methylated by an excess of thionyl-chloride in absolute methanol. When pure methylated 6-aminocaproic acid was obtained, the second method was used to achieve the corresponding urazole. Unfortunately, the ^{1}H-NMR showed again side products after the first step, which could not be assigned by LC-MS. Therefore, route B was repeated (see III.2.3) with regular 6-aminocaproic acid and again after the first step, impurities were detected in the ^{1}H-NMR spectrum. Furthermore, in the LC-MS spectrum of the semicarbazide, the obtained masses could not be assigned to possible side products.

Because a sustainable synthesis towards the urazole and the corresponding linear polymer was desired and no straightforward solution for the synthesis of caproic acid urazole could be found, another synthesis route, directly starting from citronellyl urazole, was investigated.

Linear polymers via direct polymerization of citronellyl urazole As the synthesis of a urazole requires an amine, the alcohol functionality of citronellol should first be converted into an amine. In our case, the Mitsunobu reaction was chosen[124], although recently, more sustainable alternatives are available which could be industrially more relevant.[125,126] In 2016, Cramail and co-workers reported a successful synthesis of primary amines via nitrile intermediates. When the primary amine was synthesized via the Mitsunobu reaction, the urazole was formed via the second reaction pathway (route B). After oxidation, polymerization would occur in order to obtain the linear polymer (Figure III.20).

Synthesis of citronellyl amine via the Mitsunobu reaction

To obtain the corresponding urazole, the alcohol functionality was converted into an amine via the Mitsunobu reaction. This reaction occurs in two steps, where the citronellyl phthalimide was obtained in the first step (Figure III.21a), which is further converted towards citronellyl amine with hydrazine (Figure III.21b). In this case, diethyl azodicarboxylate (DEAD) was chosen as azodicarboxylate in the first reaction step, which

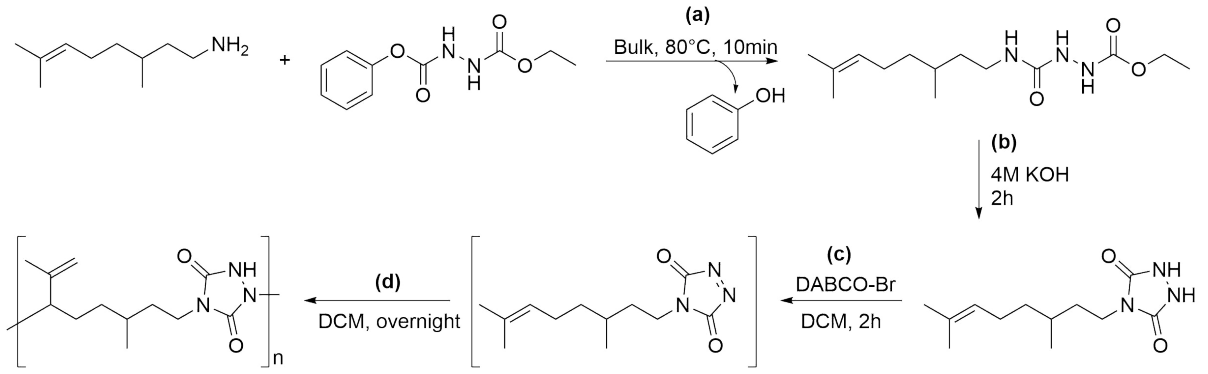


Figure III.20: (a) Semicarbazide formation between citronellyl amine and EPHD according to step 1 of route B and (b) basic cyclization in KOH towards the citronellyl urazole. (c) Oxidation of the urazole to the citronellyl TAD compound with DABCO-Br results in (d) direct polymerization of the TAD compound to a linear polymer.

reacts with triphenylphosphine to generate a phosphonium intermediate. Subsequently, this phosphonium intermediate deprotonates phthalimide, which then reacts via an S_N2 reaction with the deprotonated citronellol by DEAD, to finally obtain the citronellyl phthalimide.

Citronellyl phthalimide was obtained after column chromatography with a minor fraction of triphenylphospine oxide, which was no problem for the next reaction. For the second step, the cleavage was performed by hydrazine, which resulted in the formation of citronellyl amine and phthalylhydrazine. Because of the formation of a range of side products, such as phthalylhydrazine and triphenylphosphine oxide, the atom economy (AE) decreases and makes the total synthesis less sustainable. Therefore, other synthesis routes should be tested, but because of the limited time span and the successful synthesis of amines, the Mitsunobu reaction was maintained. After the work-up, pure citronellyl amine was obtained, with an overall yield of 69 %.

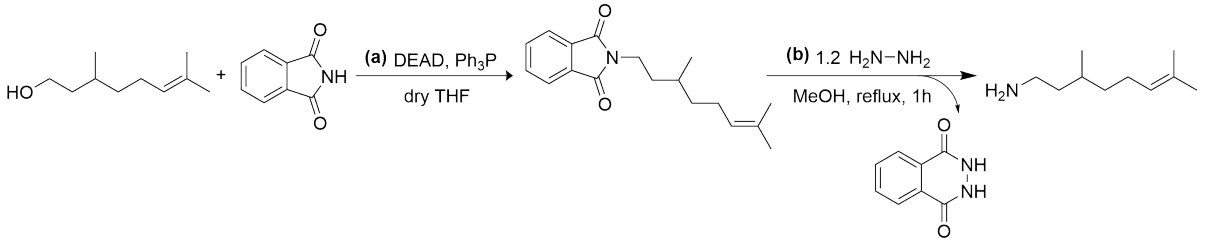


Figure III.21: Conversion of citronellol into citronellyl amine via the Mitsunobu reaction.

Synthesis of citronellyl urazole

With the pure unsaturated amine, the urazole could be formed via route A or B. In this case, route B was chosen because this synthesis route requires a shorter reaction time and the formation of the urea side product is avoided, which generally leads to higher yields. In the first step, the semicarbazide was immediately formed via reaction between citronellyl amine and EPHD at 80 °C for 10 minutes (Figure III.20a). In the reaction mixture, phenol and a minor fraction of citronellyl amine was present. Because the purity of the urazole is extremely important to obtain high molecular weights, flash column chromatography was performed to purify this intermediate.

The cyclization was performed in 4M KOH for two hours (Figure III.20b). The choice of this cyclization method will be explained in more detail in III.3.3.2. NMR showed that a side product was formed because of the harsh reaction conditions of the cyclization method (Figure III.22). The ethoxycarbonyl of the semicarbazide was hydrolyzed and followed by a decarboxylation, which finally resulted in a hydrazinocarboxylate (II.2.3.2). This side reaction is known to occur in sterically hindered semicarbazides or when the R-group is strongly electron withdrawing.[59] Although this is not the case in this reaction, it did occur anyway. This could maybe be avoided by shortening the reaction time of the basic cyclization. However, the side product could be easily removed via recrystallization in EtOAc, lowered the yield of the reaction, leading to a yield of 58 % citronellyl urazole.

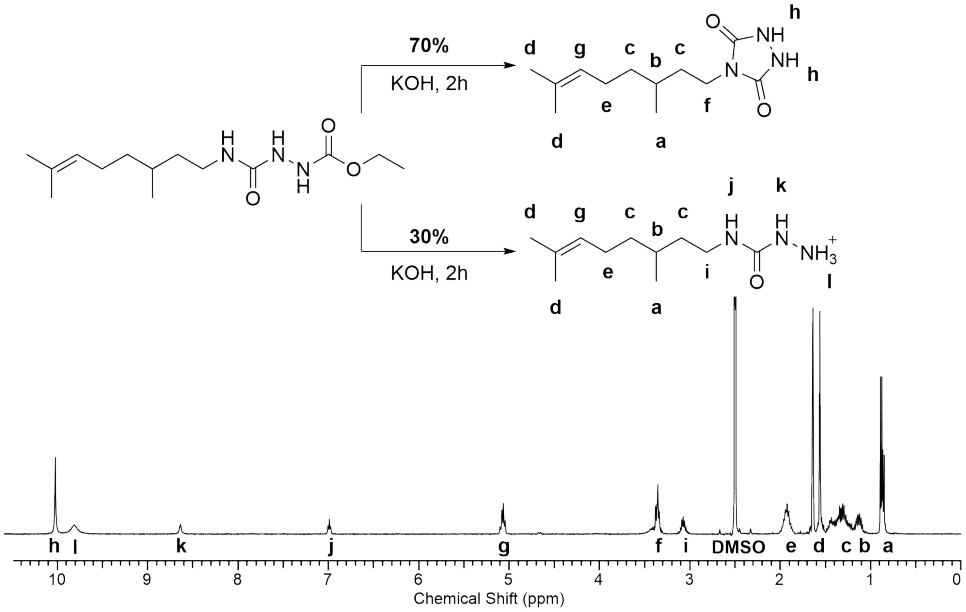


Figure III.22: Product and side product of the cyclization of citronellyl semicarbazide.

Oxidation and polymerization

Because the oxidation of oleyl urazole with NBS resulted in a mixture of polymer and NBS, the oxidation of citronellyl urazole towards citronellyl TAD was directly performed with DABCO-Br in order to avoid the same difficulties (Figure III.20c). After filtration, the solution was further stirred overnight at RT. The red color disappeared, which indicated that all TAD was consumed (Figure III.20d).

Characterization of the resulting polymer was done via NMR and SEC. Again, quantitative analysis of NMR spectra was proven to be difficult as overlap in peaks occurred. SEC in THF showed an M_n of only 780 g/mol and a dispersity of 1.3. Afterwards, SEC in DMA was performed with LiCl salts to break possible hydrogen bonds. This resulted in an equally low M_n of 1100 g/mol with a dispersity of 2.6. The low molecular weight was not expected, but could however be foreseen, as the reaction mixture stayed red for a long period of time, while AE-reaction on model compound scale was a fast process that was finished within seconds. Therefore, a further investigation in literature showed that DABCO-Br can also be used as a strong brominating agent.[65] Next to the oxidation of an alcohol towards carbonyl compounds[48], DABCO-Br can provide the bromination of various organic compounds like aromatic compounds and alkenes.[127–129] An ^{1}H-NMR analysis showed that this could be the case with the substituted alkene because new peaks appear at 1.81 and 1.91 ppm, which could represent the CH_3 next to the bromine and a peak at 4.01 ppm, which could represent the CH where the second bromine is added.

It is thus important to mention that, for the case of citronellyl amine, the synthesis of the AB-monomer was successful. However, other oxidation methods should be investigated in order to avoid the bromination of the alkenes. Possible other oxidation strategies could be silica-supported nitric acid, which has been proven to be compatible with propargyl-ethers.[130]

III.3.3 Hyperbranched polymers

III.3.3.1 Introduction

The interest in HPs is high, because of their promising applications, ranging from the biomedical sector to coatings, but unfortunately, nowadays, most of the HPs are based

on fossil resources (II.3.3). To improve the sustainability, this project focussed on the synthesis of HPs based on renewable starting materials, mainly terpenes. Furthermore, the sustainability of the HPs was increased by their easy one-pot synthesis process. Moreover, the large number of terminal functional groups offers the possibility for further modifications, yielding a broad application window.

III.3.3.2 Geraniol

The research leading to this chapter was performed in parallel to the previous paragraphs, investigating the use of citronellol in linear polymers. Therefore, both the outline of this chapter as the previously mentioned challenges will be similar. However, in this case, the synthesis of an AB_2 monomer was envisioned to obtain hyperbranched polymers in a one-pot process. In this case, as renewable starting compound, geraniol was chosen, which has a similar structure as citronellol but with an additional double bond, which results in the AB_2 functionality.

Reaction of PhTAD with geraniol The same model experiment as performed with citronellol was repeated with geraniol, in which now two equivalents of PhTAD were used for reaction with the two unsaturations. In this case, the color change took a longer time, as overnight reaction was necessary. The longer reaction time may be explained by the increased sterical hindrance that arises after one addition to geraniol. Figure III.23 shows the ^{1}H-NMR spectra of the resulting product, which proved that an AE-reaction occurred between the TAD compound and the two double bonds because two new peaks appear at 4.49 and 4.61 ppm, which represents the protons CH_h and CH_g next to the urazole-moieties. Furthermore, two peaks at 5.01 and 5.11 ppm with each an integration of two represent the two formed terminal double bonds. Moreover, the resonances corresponding to $CH_{3,a}$ and $CH_{3,b}$ at 1.55 and 1.65 ppm, have disappeared, showing the shift of the unsaturations towards the end-standing positions. The very broad peak at 10.5 ppm has an integration of two, which represents the two acidic protons of the urazoles.

To conclude, an AE-reaction occurred between geraniol and two TAD compounds. The double bonds are again shifted towards a terminal position. As geraniol also contains an alcohol functionality, it can be used as an AB_2 monomer.

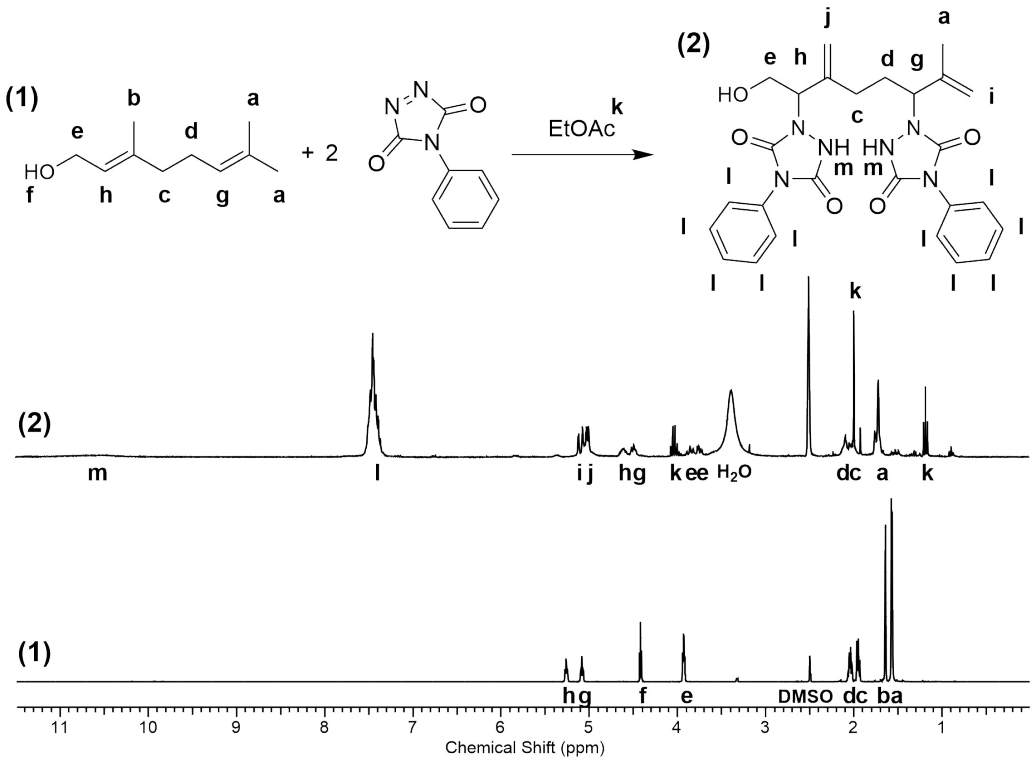


Figure III.23: ^{1}H-NMR analysis of (1) geraniol and (2) the AE-adduct of geraniol and two equivalents PhTAD.

Hyperbranched polymers via esterification reactions with geraniol A similar idea as explained in III.3.2.2 was applied in order to obtain HPs via an esterification reaction with geraniol. To obtain HPs, the monomer should have two carboxylic acids, which then could react with the alcohol functionality of geraniol. As geraniol has two double bonds which could react via an AE-reaction, a TAD compound with one carboxylic acid was necessary (Figure III.24). Again, the amino acid 6-aminocaproic acid could be an interesting amine for this purpose. But as already concluded in the case of citronellol, the synthesis towards the corresponding urazole resulted in impurities after the first step. The reaction was stopped because a direct polymerization of the citronellyl amine seemed more promising. Simultanious with citronellyl urazole, the synthesis of hyperbranched polymers was tested via a direct polymerization of geraniol urazole (Figure III.25).

Hyperbranched polymers via direct polymerization of geranyl urazole The same principle as with the linear polymer starting from citronellol is in this paragraph applied to obtain a HP from geraniol (Figure III.25). Geraniol contains two double bonds, which are available for two AE-reactions with a TAD compound, as shown above. Again,

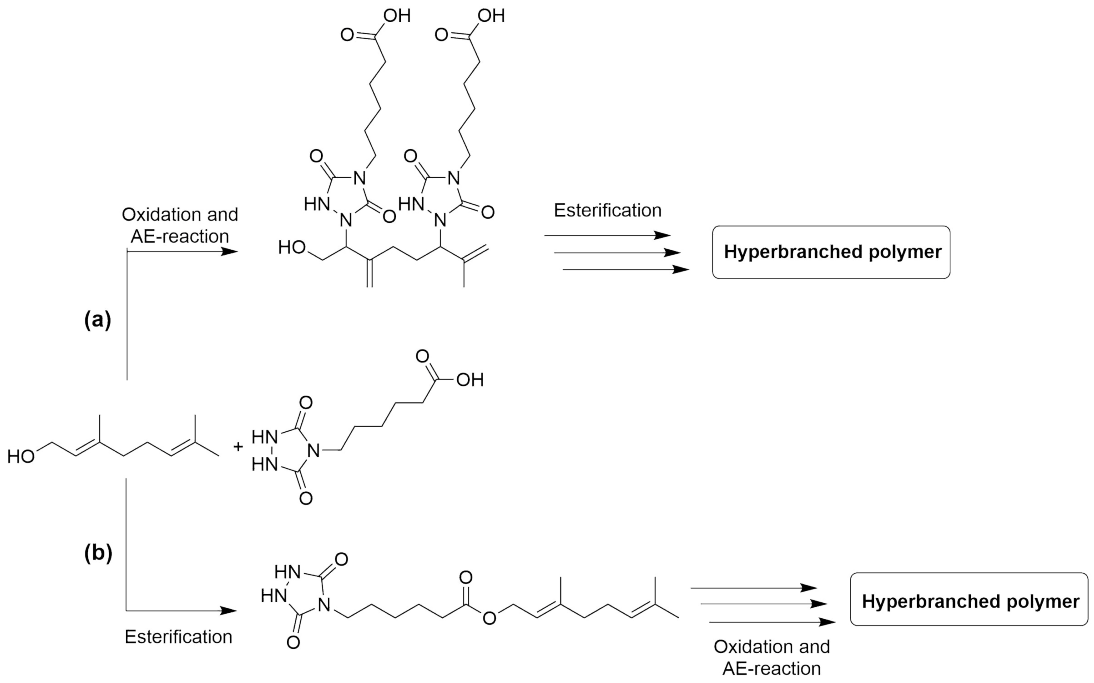


Figure III.24: Route towards HPs starting from geraniol and 6-aminocaproic acid urazole via (a) oxidation and AE-reaction, followed by esterification or (b) vice versa.

the alcohol functionality was converted into an amine via the Mitsunobu reaction and the geranyl-urazole can then be synthesized from the pure amine. After oxidation, the polymerization based on an intermolecular reaction was initiated. The color change after oxidation could be employed to follow the reaction from a TAD compound to HPs.

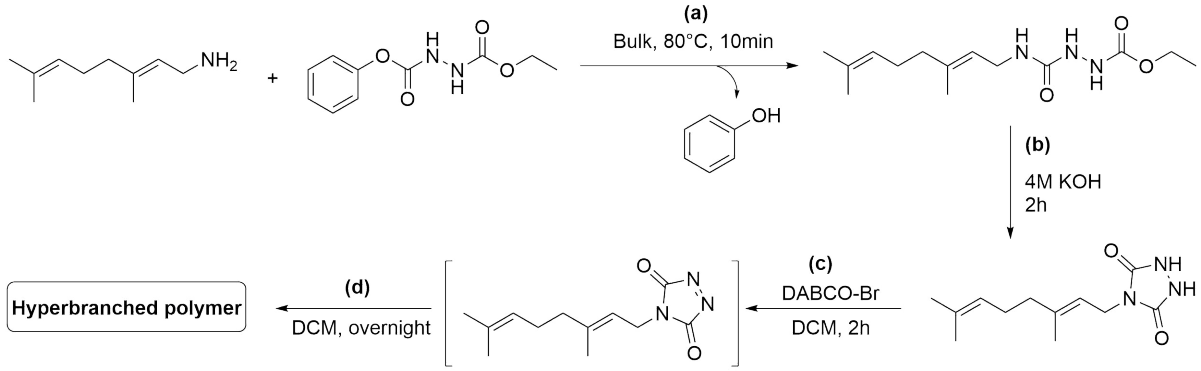


Figure III.25: (a) Semicarbazide formation between geranyl amine and EPHD according to step 1 of route B and (b) basic cyclization in KOH towards the geranyl urazole. (c) Oxidation of the urazole to the geranyl TAD compound with DABCO-Br results in (d) polymerization of the TAD compound to the HP.

Synthesis of geranyl amine via the Mitsunobu reaction

The alcohol functionality was converted into an amine via the Mitsunobu reaction to obtain the corresponding urazole (Figure III.26). Again, the reaction was performed with

DEAD and after a purification with column chromatography, pure geranyl phthalimide was obtained. The product is cleaved by hydrazine in the second step and after filtration of phthalhydrazide, pure geranyl amine was obtained with an overall yield of 68 %.

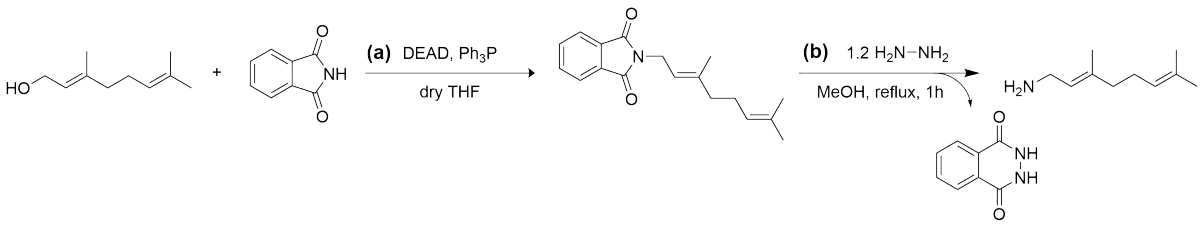


Figure III.26: Conversion of geraniol into geranyl amine via the Mitsunobu reaction.

Synthesis of geranyl urazole

The urazole with geranyl amine as starting compound was synthesized via route B, for the same reasons as in the case with citronellol. The first step included the formation of the semicarbazide via reaction between geranyl amine and the reactive intermediate EPHD (Figure III.25a). Again, phenol and a minor fraction of geranyl amine were present in the reaction mixture and to obtain a pure semicarbazide, column chromatography was performed before the cyclization was started. A yield of 51 % was obtained, which was lower than expected, because of the purification. For the cyclization towards the urazole, first a thermal cyclization was performed. NMR analysis proved that side products were formed. Therefore, in a second experiment, 10 mol% inhibitor hydroquinone was added to inhibit radical formation when the cyclization was performed at 250 °C, but still the same side products were formed. Probably, also a degradation of the product was obtained because of the high temperature of 250 °C. Because the thermal cyclization resulted in impurities, a basic cyclization was performed. First, the milder K_2CO_3 in EtOH was used. After refluxing overnight and acidification, the urazole was obtained, but again impurities were present, which was shown by an ^{1}H-NMR spectrum and LC-MS. Therefore, a cyclization in 4M KOH solution was performed, which resulted in the pure urazole (Figure III.25b). Finally, a yield of 53 % was obtained.

Oxidation and polymerization

In parallel with citronellol, the oxidation of the urazole towards the TAD compound was performed with the tetrameric complex DABCO-Br (Figure III.25c). When the oxidation was finished, after filtration, the red reaction mixture stirred overnight at RT to allow for

polymerization towards a HP (Figure III.25d). The next day, the color of the mixture turned white, which confirmed that all TAD was consumed.

Again, characterization of the resulting polymer was done via NMR and SEC. In Figure III.27, the ^{1}H-NMR spectra of the urazole monomer and the HP are showed. While the peaks of the urazole are all sharp, the peaks of the HP are much broader, which indicates the polymeric structure. Furthermore, the spectrum of the HP contains a signal at 10 ppm, which indicates the formed acidic proton after the AE-reaction. In the case of the linear polymer of citronellyl amine, the ^{1}H-NMR shows an evidence of bromination of the double bond. Here, it is more difficult to prove because the spectrum is rather complex. Because a lot of peaks appears around 4 ppm, the region of the CH containing bromine, bromination of the double bonds could indeed be the case.

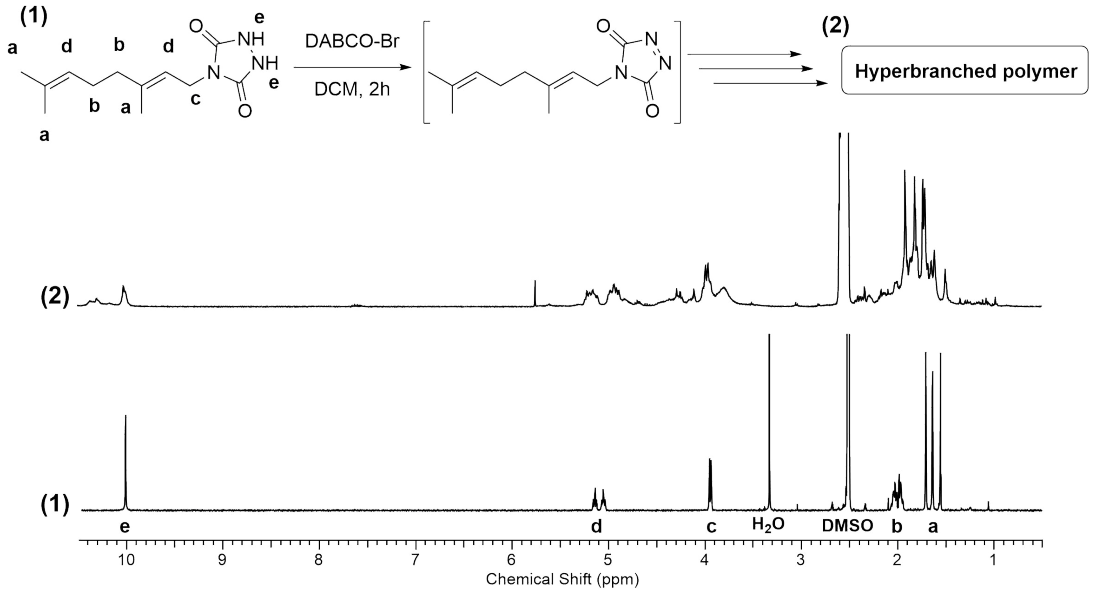


Figure III.27: ^{1}H-NMR spectra of (1) the geranyl-urazole and (2) the corresponding hyperbranched polymer.

SEC in THF showed an M_n of only 580 g/mol and a dispersity of 1.3. Afterwards, SEC in DMA was performed with LiBr salts to break possible hydrogen bonds. This resulted in an equally low M_n of 1100 g/mol with a dispersity of 1.2. The difference in M_n indicates that the polymer indeed contains hydrogen bonds, which makes the radius of the product smaller and gives the impression that the HP has a lower M_n. Just like the case of the linear polymer of citronellyl amine, the low molecular weight was not expected. However, the synthesis of the AB_2-monomer was successful and other solutions for oxidations should be investigated.

Chapter IV

Conclusion

The general aim of this master thesis was to investigate how sustainable urazoles can contribute to polymer application. The goal was twofold, as the first part was the search for a more sustainable synthesis route, without the use of isocyanates or chloroformates, towards urazoles, as precursor of a library of TAD compounds, while the second part focussed on how these sustainable compounds could be applied in polymer applications.

Concerning the first part, it can be concluded that the synthesis towards more sustainable urazoles was successful, as two one-pot isocyanate-free synthesis routes were optimized and applied to wide range of amines with different R-groups. Depending on the starting product and desired incorporated functionalities, one synthesis route is preferred over the other. Via the first method, urazoles with alkyl or related functionalities were obtained in high yield, while amines with more reactive groups posed a challenge. However, the second synthesis route offered a solution to this challenge, as nucleophilic groups such as an alcohol or thiol entity could be introduced. Furthermore, also a bis-urazole could be obtained. While the original synthesis routes of Mallakpour and Breton also result in high yields, the syntheses developed in this project are more sustainable, as chloroformates and solvents are avoided and equimolar amounts are applied, which significantly reduces the E-factor of the processes. Furthermore, the one-pot process enhances the easiness of the syntheses and strongly reduces the reaction time, as the reactions are fast, quantitative and there is no need for intermediate purification.

In a second part of this manuscript, the application of the sustainable urazoles in linear and (hyper)branched polymers was tested. As sustainability was a focus point of this work,

the synthesis towards the polymers was started from renewable starting materials with a focus on fast, one-pot reaction mechanisms. AB- and AB_2-monomers could be synthesized starting from oleylamine, citronellol and geraniol. Both citronellol and geraniol were first converted towards the corresponding amine, followed by urazole synthesis as described in the first part of this work. While the polymerization of oleyl urazole resulted in a linear polymer with a molecular weight of 3 400 g/mol, the self-condensation of citronellyl and geranyl urazole were shown to be more challenging by the competing bromination of the unsaturations in the monomer. Further research is thus needed to find an optimal oxidation method.

As a perspective, several aspects should be further investigated to promote the use of the sustainable urazoles towards polymer applications. Firstly, sustainable synthesis routes to convert alcohols, such as geraniol, into the corresponding amine should be investigated to further optimize the reaction process towards sustainable urazoles. Furthermore, it is important to investigate a range of oxidation systems in which self-condensation polymerization can occur *in situ* without side reaction such as bromination or oxidation of the unsaturations. As a range of oxidation methods for TAD are available, it should be possible to find an ideal system. Once high molecular weight (hyperbranched) polymers can be obtained, it is necessary to fully investigate the properties of these materials and their application as, for example, viscosity modifiers or coatings. As a last step, the high reactivity of TAD compounds towards dienes via a Diels-Alder approach could be incorporated to enhance the speed of the polymerization process. For example, the terpene myrcene could be a useful renewable starting material for this purpose as this has a diene and an isolated double bond Figure II.5.

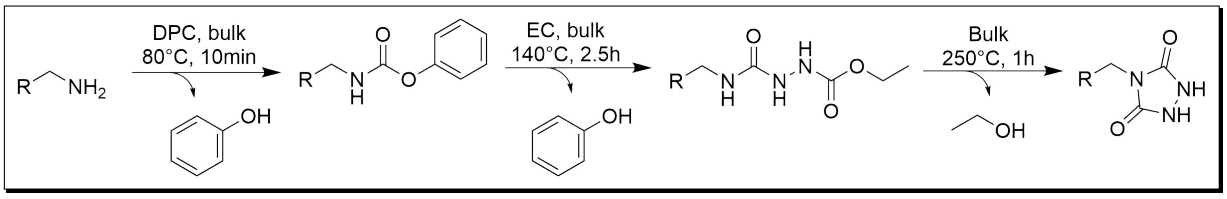
Generally, it can be conclude that this work opens the way for the sustainable synthesis towards urazoles and triazolinediones. Furthermore, we have shown that AB- and AB_2-monomers can be synthesized with the goal to obtain linear and hyperbranched polymer structures with strong hydrogen bonding properties in the polymer backbone, which could give rise to interesting polymer applications.

Appendix A

Expertimental Part

A.1 Synthesis of sustainable urazole compounds

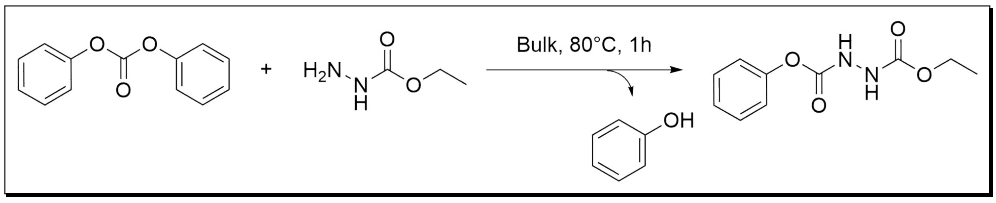
A.1.1 Synthesis route A - Via an activated carbamate



DPC (1 eq) was heated to 80 °C under inert atmosphere (N_2), in a metal bath. After melting, a primary amine (1 eq) was added and the reaction mixture stirred for 10 minutes. EC (1 eq) was added to the reaction mixture and stirred for 2.5 h at 140 °C. The reaction mixture was further heated for 1 h at 250 °C under a gentle nitrogen flow. The pure product was obtained.

A.1.2 Synthesis route B - Via an activated intermediate

A.1.2.1 Synthesis of ethyl phenyl hydrazine-1,2-dicarboxylate (EPHD)



20 g DPC (1 eq, 93 mmol) was melted in a 250 mL flask. 20 g EC (2 eq, 0.192 mol) was added and the mixture stirred under inert atmosphere for 1 h at 80 °C. The product was precipitated in water, dried under vacuum at 40 °C and the pure white powder was obtained.

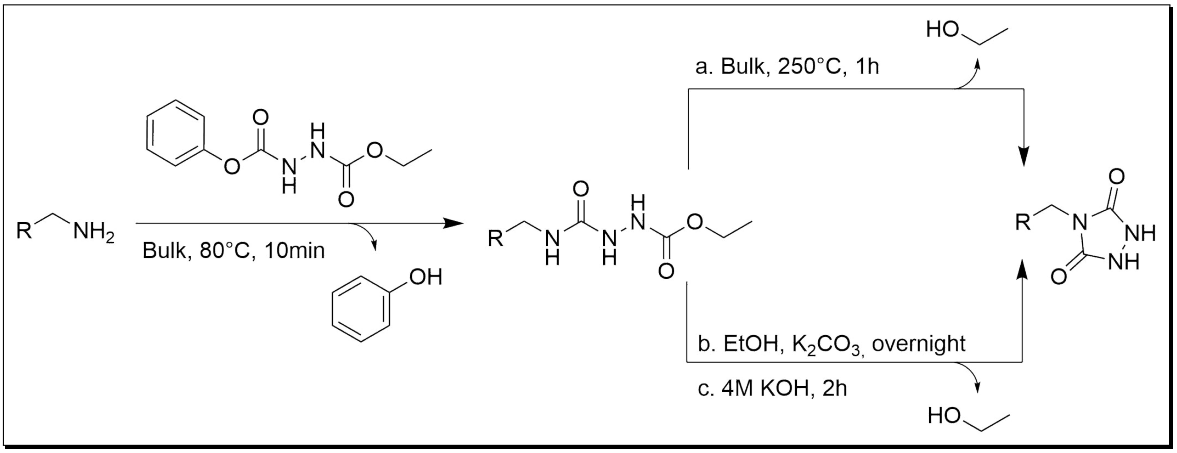
Yield: 76%

Chemical formula: $C_{10}H_{12}N_2O_4$

Molecular weight: 224.22 g/mol

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.17 (t, 3 H, O−CH_2−CH_3), 4.08 (q, 2 H, O−CH_2−CH_3), 7.01-7.47 (m, 5 H, Ar−*H*), 9.25 (s, 1 H, N*H*−CO−O−Et), 9.67 (s, 1 H, Ar−O−CO−N*H*).

A.1.2.2 Synthesis of urazole components



EPHD (1 eq) was melted at 80 °C under inert atmosphere (N_2). A primary amine (1 eq) was added and the mixture was stirred for 10 minutes. Subsequently, the temperature of the reaction mixture was increased to 250 °C for 1 h and a gentle nitrogen flow was applied. The pure product was obtained. For functional amines, a basic cyclization was applied. In that case, after stirring for 10 minutes, K_2CO_3 (5 eq) in ethanol was added and refluxed overnight under inert atmosphere (N_2). After cooling the reaction mixture to RT, HCl in 2-propanol (5-6 N) was added to lower the pH to 1-2. The precipitate was filtered off and the reaction mixture was concentrated *in vacuo* to obtain the pure product. Furthermore, in a third cyclization, 4M KOH (2 eq) was added and refluxed for 2 hours. Again, to lower the pH, 1M HCl solution was added and after filtration, the residue was dried to obtain the pure product.

A.1.3 Urazoles via route A and B

A.1.3.1 Butylamine

Carbamate

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 0.89 (t, 3 H, CH_2-CH_3), 1.32 (sext, 2 H, $CH_2-CH_2-CH_3$), 1.45 (quint, 2 H, $CH_2-CH_2-CH_3$), 3.06 (q , 2 H, CH_2-CH_2-NH), 5.71 (t, 0.1 H, urea), 6.74-7.41 (m, 10 H, Ar−*H*), 7.72 (t, 1 H, CH_2-CH_2-NH), 9.30 (s, 1 H, PhO*H*).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.85 (t, 3 H, CH_2-CH_3), 1.17 (t, 3 H, $O-CH_2-CH_3$), 1.26 (sext, 2 H, $CH_2-CH_2-CH_3$), 1.35 (quint, 2 H, $CH_2-CH_2-CH_3$), 2.98 (q, 2 H, CH_2-CH_2-NH), 4.02 (q, 2 H, CH_3-CH_2-O), 5.71 (t, 0.1 H, urea), 6.27 (s, 1 H, $CH_2-NH-CO$), 6.7-7.2 (m, 10 H, Ar-*H*), 7.61 (s, 1 H, $O-CO-NH$), 8.71 (s, 1 H, $NH-NH-CO-NH$), 9.32 (s, 2 H, PhO*H*).

Urazole

Yield: A = 86 %, B = 89 %

Chemical formula: $C_6H_{11}N_3O_2$

Molecular weight: 157.17 g/mol

LC-MS (m/z): 156.1 $[M-H]^-$

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.88 (t, 3 H, CH_2-CH_3), 1.25 (sext, 2 H, $CH_2-CH_2-CH_3$), 1.50 (quint, 2 H, $CH_2-CH_2-CH_3$), 3.35 (q, 2 H, CH_2-CH_2-NH), 10.00 (s, 2 H, $NH-NH$).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 13.34 (CH_3), 19.25 (CH_2), 29.55 (CH_2), 37.55 (CH_2), 155.17 (CO).

A.1.3.2 Octylamine

Carbamate

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.85 (t, 3 H, CH_2-CH_3), 1.27 (d, 10 H, $(CH_2)_5-CH_3$), 1.43 (t, 2 H, CH_2-CH_2-NH), 3.04 (q, 2 H, CH_2-NH), 5.69 (t, 1 H, $CH_2-NH-CO$), 6.7-7.41 (m, 10 H, Ar−*H*), 9.18 (s, 1 H, PhO*H*).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.85 (t, 3 H, CH_2−CH_3), 1.17 (t, 3 H, O−CH_2−CH_3), 1.25 (s, 10 H, (CH_2)$_5$−CH_3), 1.35 (t, 2 H, CH_2−CH_2−NH), 2.97 (q, 2 H, CH_2−NH), 4.02 (q, 2 H, O−CH_2−CH_3), 6.26 (t, 1 H, NH−CH_2−CH_2), 6.7-7.2 (m, 5 H, Ar−H), 7.60 (s, 1 H, O−CO−NH), 8.69 (s, 1 H, NH−NH−CO−NH), 9.27 (s, 1 H, PhOH).

Urazole

Yield: A = 96 %, B = 95 %

Chemical formula: $C_{10}H_{19}N_3O_2$

Molecular weight: 213.28 g/mol

LC-MS (m/z): 214.2 $[MH]^+$

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.85 (t, 3 H, CH_2−CH_3), 1.24 (m, 10 H, (CH_2)$_5$−CH_3), 1.51 (quint, 2 H, N−CH_2−CH_2), 3.35 (t, 2 H, N−CH_2), 10.00 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 13.90 (CH_3), 22.04 (CH_2), 26.00 (CH_2), 27.38 (CH_2), 28.40 (CH_2), 28.55 (CH_2), 31.13 (CH_2), 37.80 (CH_2), 155.00 (CO).

A.1.3.3 Benzylamine

Carbamate

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 4.28 (d, 2 H, Ar−CH_2), 6.7-7.73 (m, 15 H, Ar-H), 8.31 (t, 1 H, Ar−CH_2−NH), 9.32 (s, 1 H, PhOH).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.18 (t, 3 H, O−CH_2−CH_3), 4.04 (q, 2 H, O−CH_2−CH_3), 4.22 (d, 2 H, Ar−CH_2−NH), 6.7-7.73 (m, 15 H, Ar-H), 6.91 (s, 1 H, CH_2−NH−CO), 7.82 (s, 1 H, O−CO−NH), 8.82 (s, 1 H, NH−NH−CO−NH), 9.31 (s, 2 H, PhOH).

Urazole

Yield: A = 87 %, B = 85 %

Chemical formula: $C_9H_9N_3O_2$

Molecular weight: 191.19 g/mol

LC-MS (m/z): 190 $[M\text{-}H]^-$

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 4.54 (s, 2 H, Ar−CH_2−N), 7.2-7.4 (m, 5 H, Ar−H), 10.18 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 41.20 (CH_2), 127.46 (CH), 128.44 (CH), 136.69 (C), 154.73 (CO).

A.1.3.4 Tetrahydrofurfurylamine

Carbamate

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.56 (m, 1 H, CH_2−CH_2−CH_2), 1.82 (m, 2 H, CH_2−CH_2−CH_2), 1.92 (m, 1 H, CH_2−CH_2−CH_2), 3.10 (t, 2 H, CH−CH_2−NH), 3.63 (q, 1 H, O−CH_2−CH_2), 3.75 (quint, 1 H, O−CH_2−CH_2), 3.89 (quint, 1 H, O−CH−CH_2), 6.7-7.42 (m, 10 H, Ar−H), 7.82 (t, 1 H, CH_2−NH), 9.31 (s, 1 H, PhOH).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.16 (t, 3 H, O−CH_2−CH_3), 1.50 (m, 1 H, CH_2−CH_2−CH_2), 1.80 (m, 3 H, CH_2−CH_2−CH_2), 3.05 (m, 2 H, CH−CH_2−NH), 3.60 (q, 1 H, O−CH_2−CH_2), 3.74 (q, 1 H, O−CH_2−CH_2), 3.80 (t, 1 H, O−CH−CH_2), 4.02 (q, 2 H, O−CH_2−CH_3), 6.24 (t, 1 H, CH_2−NH−CO), 6.74-7.2 (d, 10 H, Ar−H), 7.71 (s, 1 H, O−CO−NH), 8.75 (s, 1 H, NH−NH−CO−NH), 9.31 (s, 2 H, PhOH).

Urazole

Yield: A = 87 %, B = 90 %

Chemical formula: $C_7H_{11}N_3O_3$

Molecular weight: 185.18 g/mol

LC-MS (m/z): 186.1 $[MH]^+$, 184 $[M\text{-}H]^-$

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.60 (m, 1 H, CH_2−CH_2−CH_2), 1.83 (m, 3 H, CH_2−CH_2−CH_2), 3.39 (m, 2 H, CH−CH_2−NH), 3.62 (q, 1 H, O−CH_2−CH_2), 3.73 (q, 1 H, O−CH_2−CH_2), 3.80 (t, 1 H, O−CH−CH_2), 10.03 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 24.73 (CH_2), 28.52 (CH_2), 41.87 (CH_2), 66.93 (CH_2), 74.85 (CH), 155.03 (CO).

A.1.3.5 Oleylamine

Carbamate

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.89 (t, 3 H, CH_2-CH_3), 1.30 (d, 22 H, $_{11}$xCH_2), 1.58 (t, 2 H, CH_2-CH_2-NH), 2.03 (q, 4 H, $CH_2-CH=CH-CH_2$), 3.26 (q, 2 H, CH_2-CH_2-NH), 5.08 (s, 1 H, $CH_2-NH-CO$), 5.35 (t, 2 H, $CH=CH$), 6.76-7.43 (m, 10 H, Ar$-H$).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO$-d_6$): δ (ppm) = 0.86 (t, 3 H, CH_2-CH_3), 1.17 (t, 3 H, $O-CH_2-CH_3$), 1.24 (m, 24 H, 12x(CH_2)), 2.01 (q, 4 H, $CH_2-CH=CH-CH_2$), 2.97 (q, 2 H, CH_2-CH_2-NH), 4.02 (d, 2 H, $O-CH_2-CH_3$), 5.33 (t, 2 H, $CH=CH$), 6.26 (t, 1 H, $CH_2-NH-CO$), 6.69-7.21 (m, 10 H, Ar$-H$), 7.60 (s, 1 H, $O-CO-NH$), 8.67 (s, 1 H, $NH-NH-CO-NH$).

Urazole

Yield: A = 96 %, B = 95 %

Chemical formula: $C_{20}H_{37}N_3O_2$

Molecular weight: 351.54 g/mol

LC-MS (m/z): 352.3 $[MH]^+$, 350,2 $[M-H]^-$

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.86 (t, 3 H, CH_2-CH_3), 1.24 (d, 22 H, 11 xCH_2), 1.66 (t, 2 H, CH_2-CH_2-NH), 2.01 (q, 4 H, $CH_2-CH=CH-CH_2$), 3.53 (q, 2 H, CH_2-CH_2-NH), 5.35 (t, 2 H, $CH=CH$), 9.96 (s, 2 H, $NH-NH$).

^{13}C-NMR (400 MHz, $CDCl_3$): δ (ppm) = 13.92 (CH_3), 22.11 (CH_2), 26.00 (CH_2), 26.55 (CH_2), 27.42 (CH_2), 28.48 (CH_2), 28.52 (CH_2), 28.55 (CH_2), 28.66 (CH_2), 28.74 (CH_2), 28.80 (CH_2), 29.00 (CH_2), 29.07 (CH_2), 31.25 (CH_2), 37.80 (CH_2), 129.61 (CH), 130.05 (CH), 155.03 (CO).

A.1.3.6 Allylamine

Carbamate

^{1}H-NMR (300 MHz, DMSO$-d_6$): δ (ppm) = 3.69 (t, 2 H, $CH-CH_2-NH$), 5.15 (m, 2 H, $CH=CH_2$), 5.85 (m, 1 H, $CH=CH_2$), 6.7-7.42 (m, 10 H, Ar$-H$), 7.93 (t, 1 H, $CH_2-NH-CO$), 9.31 (s, 1 H, PhOH).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.16 (t, 3 H, O−CH_2−CH_3), 3.63 (t, 2 H, CH−CH_2−NH), 4.02 (q , 2 H, O−CH_2−CH_3), 5.05 (m, 2 H, CH=CH_2), 5.79 (m, 1 H, CH=CH_2), 6.48 (t, 1 H, CH_2−NH−CO), 6.7-7.22 (m, 10 H, Ar−H), 7.73 (s, 1 H, O−CO−NH), 8.76 (s, 1 H, NH−NH−CO−NH), 9.30 (s, 2 H, PhOH).

Urazole

Yield: A = 89 %, B = 84 %

Chemical formula: $C_5H_7N_3O_2$

Molecular weight: 141.13 g/mol

LC-MS (m/z): 283.1 $[MH]^+$, 281 $[2M\text{-}H]^-$, 422,1 $[3M\text{-}H]^-$

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 3.95 (t, 2 H, CH−CH_2−NH), 5.11 (m, 2 H, CH=CH_2), 5.80 (m, 1 H, CH=CH_2), 10.11 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 116.45 (CH_2), 132.27 (CH), 154.59 (CO).

A.1.3.7 Cyclohexanemethylamine

Carbamate

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.9 (t, 2 H, CH_2−CH_2−CH_2−CH_2−CH_2), 1-1.75 (m, 9 H, CH_2−CH_2−CH−CH_2−CH_2), 3.17 (t, 2 H, CH_2−NH), 6.7-7.4 (m, 10 H, Ar−H), 7.84 (t, 1 H, CH_2−NH−CO), 9.60 (s, 1 H, PhOH).

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.9 (t, 2 H, CH_2−CH_2−CH_2−CH_2−CH_2), 1.04-1.77 (m, 12 H, CH_2−CH_2−CH−CH_2−CH_2andO−CH_2−CH_3), 2.85 (t, 2 H, CH_2−NH), 4.02 (q, 2 H, O−CH_2−CH_3), 6.27 (t, 1 H, CH_2−NH−CO), 6.7-7.22 (m, 10 H, Ar−H), 7.57 (s, 1 H, O−CO−NH), 8.70 (s, 1 H, NH−NH−CO−NH), 9.30 (s, 2 H, PhOH).

Urazole

Yield: A = 93 %, B = 95 %

Chemical formula: $C_9H_{15}N_3O_2$

Molecular weight: 197.24 g/mol

LC-MS (m/z): 198.1 $[MH]^+$, 196,1 $[M\text{-}H]^-$

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 0.90 (t, 2 H, CH_2−CH_2−CH_2−CH_2−CH_2), 1.04-1.73 (m, 9 H, CH_2−CH_2−CH−CH_2−CH_2), 3.19 (t, 2 H, CH_2−N), 10.00 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 25.07 (CH_2), 25.88 (CH_2), 30.03 (CH_2), 35.91 (CH), 43.75 (CH_2), 155.24 (CO).

A.1.4 Urazoles via route B

A.1.4.1 3-Amino-1-propanol

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.17 (t, 3 H, O−CH_2−CH_3), 1.52 (quint, 2 H, CH_2−CH_2−CH_2), 3.05 (q , 2 H, CH_2−NH), 3.38 (q, 2 H, HO−CH_2), 4.03 (q, 2 H, O−CH_2−CH_3), 4.41 (t, 1 H, HO−CH_2), 6.31 (s, 1 H, CH_2−NH), 6.7-7.2 (m, 5 H, Ar−H), 7.68 (s, 1 H, O−CO−NH), 8.75 (s, 1 H, NH−NH−CO−NH), 9.30 (s, 1 H, PhOH).

Urazole

Yield: 78 %

Chemical formula: $C_5H_9N_3O_3$

Molecular weight: 159.15 g/mol

LC-MS (m/z): 160 $[MH]^+$, 158.05 $[M\text{-}H]^-$

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 0.77 (quint, 2 H, CH_2−CH_2−CH_2), 1.6 (m, 4 H, CH_2−CH_2−CH_2), 9.12 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 31.00 (CH_2), 35.60 (CH_2), 58.30 (CH_2), 155.10 (CO).

A.1.4.2 Ethylenediamine

Semicarbazide

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 1.17 (t, 6 H, O−CH_2−CH_3), 3.05 (t, 4 H, CH_2−CH_2), 4.02 (q, 4 H, O−CH_2−CH_3), 6.43 (s, 2 H, NH−CH_2−CH_2−NH), 6.7-7.2 (m, 10 H, Ar−H), 7.78 (s, 2 H, O−CO−NH), 8.72 (s, 2 H, NH−NH−CO−NH), 9.28 (s, 2 H, PhOH).

Urazole

Yield: 92 %

Chemical formula: $C_6H_8N_6O_4$

Molecular weight: 228.17 g/mol

LC-MS (m/z): insoluble

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 3.55 (s, 4 H, CH_2−CH_2), 10.03 (s, 4 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 36.5 (CH_2), 154.6 (CO).

A.1.4.3 Cysteamine

Semicarbazide

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.17 (t, 3 H, O−CH_2−CH_3), 2.48 (m, 2 H, HS−CH_2−CH_2), 3.15 (q, 2 H, HS−CH_2−CH_2), 4.02 (q, 2 H, O−CH_2−CH_3), 6.56 (t, 1 H, NH−CH_2), 6.7-7.2 (m, 5 H, Ar−H), 7.80 (s, 1 H, O−CO−NH), 8.67 (s, 1 H, NH−NH−CO−NH).

Urazole

Yield: 27%

Chemical formula: $C_4H_7N_3O_2S$

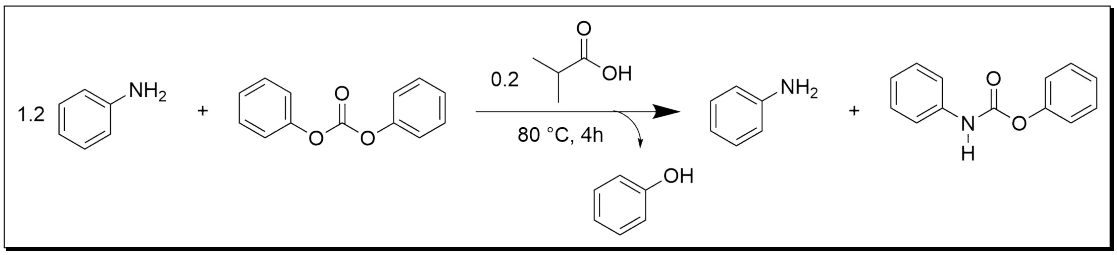
Molecular weight: 161.18 g/mol

LC-MS (m/z): insoluble

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 2.96 (t, 2 H, HS−CH_2), 3.66 (t, 2 H, HS−CH_2−CH_2), 10.11 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 35.07 (CH_2), 37.17 (CH_2), 154.80 (CO).

A.1.5 Synthesis of activated carbamate with aniline



2.14 g DPC (1 eq, 10 mmol) was melted under inert atmosphere (N_2) in an oil bath at 80 °C. After melting, 1.1 mL aniline (1.2 eq, 12 mmol) and 0.18 mL isobutyric acid (0.2 eq, 2 mmol) were added and stirred for 4 h. The mixture was dissolved in DCM (10 mL) and extracted with 4M KOH (2 x 2 mL) and brine (1 x 1 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The product and an excess of aniline were obtained.

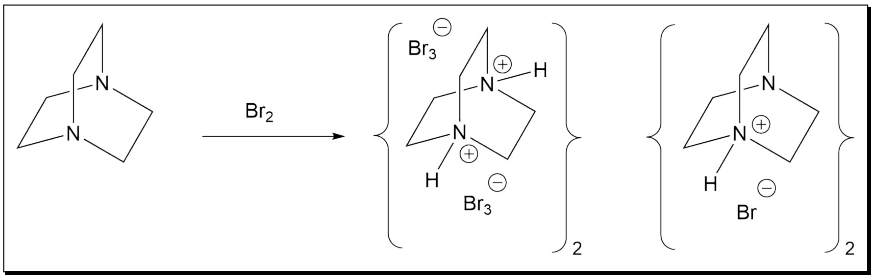
Yield: 24%

Chemical formula: $C_{13}H_{11}NO_2$

Molecular weight: 213.24 g/mol

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 6.7-7.55 (m, 10 H, Ar−*H*), 10.20 (s, 1 H, N*H*−CO).

A.1.6 Synthesis of tetrameric 1,4-diazabicyclo[2.2.2]octane bromide complex



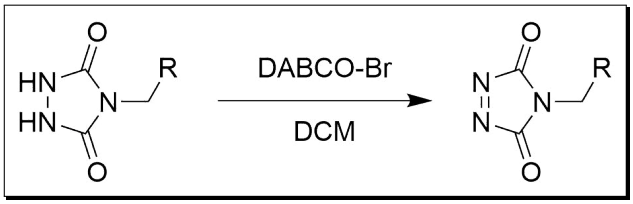
In a 250 mL flask, 6.73g 1,4-diazabicyclo[2.2.2]octane (1 eq, 60 mmol) was solubilized in 100 mL chloroform. A solution of 20 g bromine (2.1 eq, 0.125 mol) in 100 mL chloroform was added dropwise to the DABCO and stirred for 1 h under inert atmosphere (N_2). The yellow precipitate was filtered and washed with 50 mL chloroform. The product was dried under vacuum overnight at 40 °C.

Yield: 99%

Chemical formula: $C_{24}H_{54}Br_{14}N_8$

Molecular weight: 1573.4 g/mol

A.1.7 Oxidation of a urazole

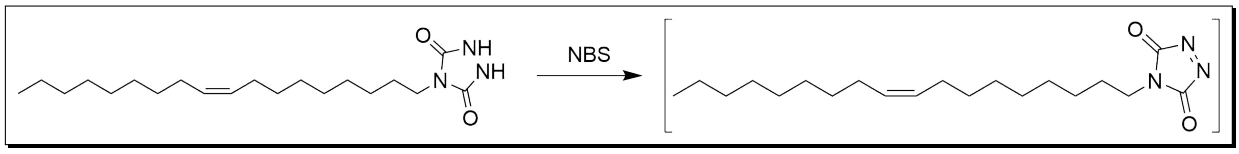


The urazole (1 eq), DABCO-Br (0.2 eq) in DCM were mixed in a flask under inert atmosphere (N_2) and stirred for 2 h at RT. The mixture was filtrated and the residue was washed with DCM. The filtrate was concentrated *in vacuo*.

A.2 Applications of sustainable urazoles in polymers

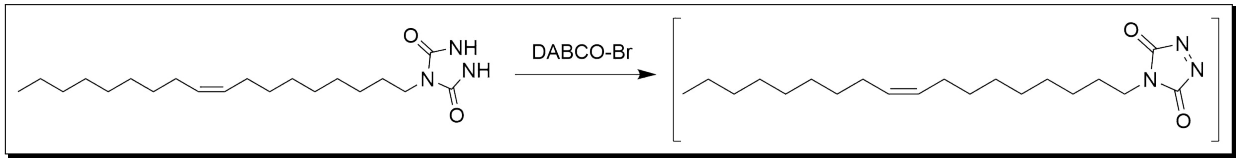
A.2.1 Linear polymers

A.2.1.1 Oxidation of oleyl urazole with NBS



A mixture of 0.5 g N-bromosuccinimide (NBS) (1 eq, 2.85 mmol) and 0.23 mL dry pyridine (1 eq, 2.85 mmol) in dry THF was added to 1 g oleyl urazole (1 eq, 2.85 mmol) in THF. After stirring overnight, the red solution became white. The reaction mixture was filtrated and concentrated *in vacuo*. The product contained NBS.

A.2.1.2 Oxidation oleyl urazole with DABCO-Br



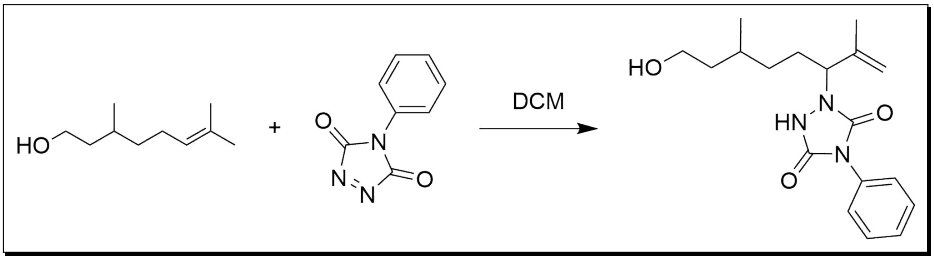
1.31 g oleyl urazole (1 eq, 3.73 mmol) was solubilized in 35 ml dichloromethane (DCM) under inert atmosphere (N_2). 1.17 g DABCO-Br (0.2 eq, 0.75 mmol) was added to the mixture and stirred for 2 h at RT. The mixture was filtrated and the residu was washed with 30 ml DCM. The filtrate was shortly concentrated *in vacuo*. The solution was further stirred overnight en subsequently concentrated *in vacuo*.

Molecular weight (THF-SEC): 3400 g/mol

T_g (DSC): -8 °C

T_{deg} (TGA): 205 °C

A.2.1.3 Alder-ene reaction between PhTAD and citronellol



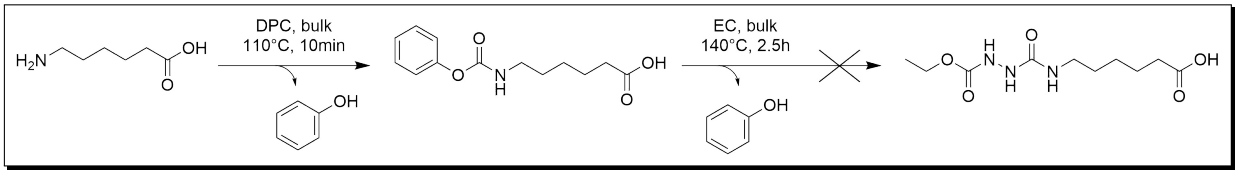
In a flask of 50 mL, 1.3 g PhTAD (1 eq, 7.42 mmol) was solubilized in 25 mL DCM. 1.36 mL citronellol (1 eq, 7.42 mmol) was added to the mixture and stirred for 5 minutes. After 1 minute, the red mixture turned yellow. The solution was concentrated *in vacuo*.

Chemical formula: $C_{18}H_{25}N_3O_3$

Molecular weight: 331.42 g/mol

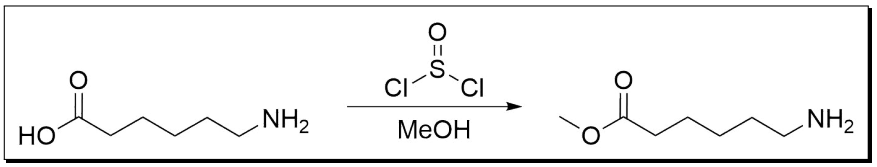
^{1}H-NMR (300 MHz, DMSO$-$d$_6$): δ (ppm) = 0.87 (d, 3 H, C$H_3$$-$CH), 1.12 (m, 1 H, CH_3-CH), 1.26 (m, 2 H, C$-$CH$-$CH$_2-CH_2$), 1.57 (m, 2 H, C$-$CH$-CH_2$), 1.72 (s, 3 H, $CH_3$$-$C), 1.80 (m, 2 H, CH$-CH_2-CH_2-$OH), 3.43 (t, 2 H, CH$-CH_2-CH_2-$OH), 4.31 (s, 1 H, CH_2-OH), 4.42 (t, 1 H, N$-$CH), 5.00 (d, 2 H, C$H_2$$-$C), 7.46 (m, 5 H, Ar), 10.82 (s, 1 H, NH).

A.2.1.4 Attempted synthesis of 6-aminocaproic acid urazole



1.07 g DPC (1 eq, 5 mmol) was heated to 110 °C in a pressure tube under inert atmosphere (N_2), in a metal bath. After melting, 0.67 g 6-aminocaproic acid (1 eq, 5 mmol) was added and the reaction mixture stirred for 10 minutes. Afterwards, 0.52 g EC (1 eq, 5 mmol) was added to the reaction mixture and stirred for 2.5 h at 140 °C. An ^{1}H-NMR showed that impurities were formed.

A.2.1.5 Methylation of 6-aminocaproic acid



A 250 mL flask was charged with 100 mL methanol and cooled in an ice bath to 0 °C. Over a period of 1 h, 6.1 mL thionylchloride (2.2 eq, 84 mmol) was slowly added and stirred for further 20 min. Then, 5 g 6-aminocaproic acid (1 eq, 38 mmol) was added and the reaction mixture stirred for 10 minutes at 0 °C and afterwards 3 h at RT. The reaction mixture was concentrated *in vacuo*, which resulted in the hydrochloric acid salt. The salt was solubilized in aqueous NaOH (1.5 eq, 57 mmol), followed by extraction with ethyl acetate (EtOAc) (2 x 100 mL). This resulted in the pure product.

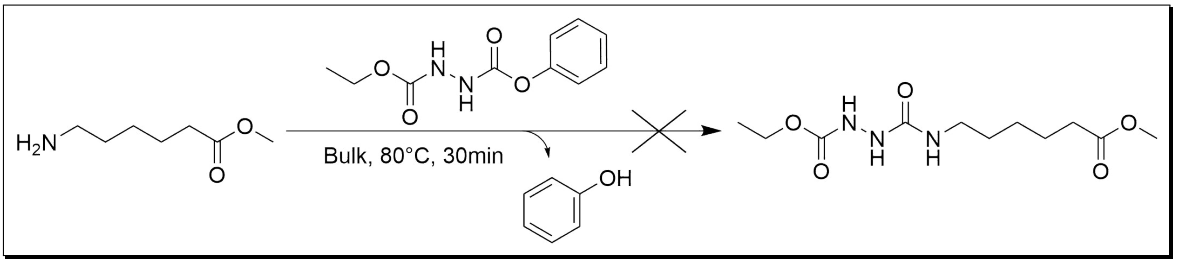
Yield: 91.4 %

Chemical formula: $C_7H_{15}NO_2$

Molecular weight: 145.2 g/mol

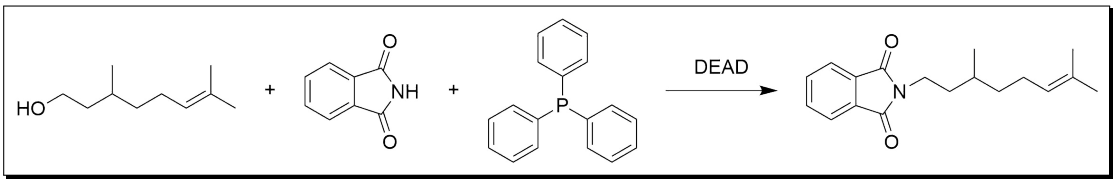
^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 1.14-1.57 (m, 8 H, CH_2−CH_2−CH_2−CH$_2$−NH_2), 2.26 (m, 4 H, CO−CH_2), 2.48 (t, 2 H, CH_2−NH$_2$), 3.58 (s, 3 H, CH_3−O).

A.2.1.6 Attempted synthesis of 6-aminocaproic acid urazole



0.86 g EPHD (1 eq, 3.86 mmol) was melted at 80 °C under inert atmosphere (N_2). 0.56 g 6-aminocaproic acid methyl ester (1 eq, 3.86 mmol) was added and the mixture was stirred for 30 minutes. ^{1}H-NMR and LC-MS showed that impurities were formed.

A.2.1.7 Synthesis of citronellylphtalimide via the Mitsunobu reaction



A mixture of 10.9 g phthalimide (1 eq, 73.9 mmol), 19.4 g triphenylphosphine (1 eq, 73.9 mmol) and 13.5 mL citronellol (1 eq, 73.9 mmol) in 50 mL of dry THF was cooled to 0 °C. 33.7 mL diethyl azodicarboxylate (DEAD) (1 eq , 73.9 mmol) in 50 ml dry THF was added dropwise over 30 minutes. The reaction mixture was then allowed to warm to RT and stirred overnight. The solvent was concentrated *in vacuo* and the residue suspended in Et_2O. The precipitate was filtered and the filtrate was concentrated *in vacuo*. Column chromatography with EtOAc as eluens was performed. Pure product was obtained, which was first liquid and subsequently crystallized very fast.

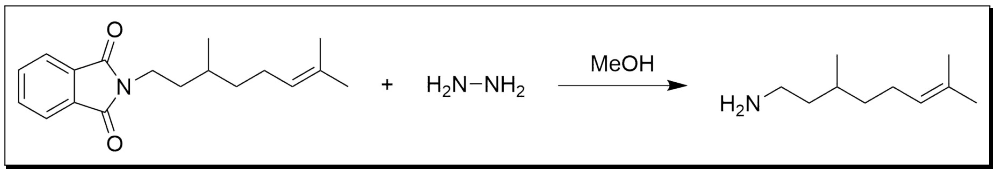
Yield: 73.3 %

Chemical formula: $C_{18}H_{23}NO_2$

Molecular weight: 285.4 g/mol

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.91 (d, 3 H, CH−CH_3), 1.1-1.45 (m, 5 H, CH_2−CH−CH_2), 1.52 (s, 3 H, C−CH_3), 1.57 (s, 3 H, C−CH_3), 1.92 (quint, 2 H, CH_2−CH=CH_2), 3.58 (t, 2 H, N−CH_2), 5.03 (t, 1 H, CH=C), 7.85 (m, 4 H, Ar−H).

A.2.1.8 Synthesis of citronellyl amine via the Mitsunobu reaction



A mixture of 6.9 g N-citronellyl-phthalimide (1 eq, 24.1 mmol) and 1.76 ml hydrazine monohydrate (1.5 eq, 0.036 mmol) in 250mL MeOH was heated at reflux for 1 h and then concentrated *in vacuo*. The residue was dissolved in 80 mL 1 M HCl and insoluble compounds were removed by filtration. The filtrate was made basic with 5M NaOH and extracted with Et_2O (3 x 250 mL). The combined ether layer was washed with saturated brine (2 x 100 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded citronellyl amine as orange/red liquid.

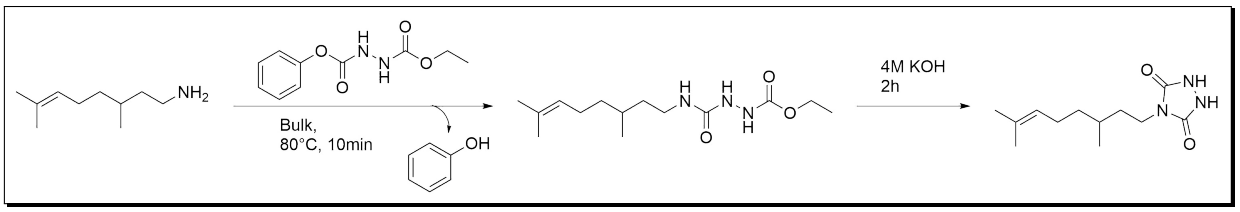
Yield: 94.7 %

Chemical formula: $C_{10}H_{21}N$

Molecular weight: 155.3 g/mol

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 0.84 (d, 3 H, CH−CH_3), 1.04-1.52 (m, 7 H, CH_2−CH−CH_2−CH_2−NH_2), 1.57 (s, 3 H, C−CH_3), 1.64 (s, 3 H, C−CH_3), 1.94 (quint, 2 H, CH_2−CH=C), 2.55 (m, 2 H, CH_2−NH_2), 5.09 (t, 1 H, CH=C).

A.2.1.9 Synthesis of citronellyl urazole



7.21 g EPHD (1 eq, 32.1 mmol) was melted at 80 °C under inert atmosphere (N_2). 5 g citronellyl amine (1 eq, 32.1 mmol) was added and the mixture was stirred for 10 minutes. Column chromatography was performed with hexane:ethyl acetate (2:1) as eluens. Subsequently, 10 mL 4 M KOH was added to the reaction mixture and refluxed for 2 h. After reaction, the mixture was cooled to RT and treated with 1 M HCl solution until pH

1 was reached. The precipitated was filtered off and dried under vacuum at 40 °C. ^{1}-NMR analysis showed that a side product was formed which was removed via a recrystallization in EtOAc. Afterwards, the pure product was obtained.

Semicarbazide

Yield: 34 %

Chemical formula: $C_{14}H_{27}N_3O_3$

Molecular weight: 285.4 g/mol

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 0.85 (d, 3 H, CH−CH_3), 1.04-1.5 (m, 8 H, CH_2−CH−CH_2,CH_2−CH_3), 1.56 (s, 3 H, CH_3−C), 1.64 (s, 3 H, CH_3−C), 1.93 (m, 2 H, C=CH−CH_2), 3.01 (quint, 2 H, CH_2−N), 4.03 (t, 2 H, CH_2−CH$_3$), 5.09 (t, 1 H, C=CH), 6.24 (s, 1 H, CH$_2$−NH−CO), 7.60 (s, 1 H, O−CO−NH), 8.70 (s, 1 H, O−CO−NH−NH).

Urazole

Yield: 58 %

Chemical formula: $C_{12}H_{21}N_3O_2$

Molecular weight: 239.3 g/mol

LC-MS (m/z): 240.1 $[MH]^+$

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 0.89 (d, 3 H, CH−CH_3), 1.04-1.43 (m, 5 H, CH_2−CH−CH_2), 1.56 (s, 3 H, CH_3−C), 1.64 (s, 3 H, CH_3−C), 1.93 (m, 2 H, C=CH−CH_2), 3.37 (t, 2 H, CH_2−N), 5.06 (t, 1 H, CH−CH$_3$), 10.00 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 17.42 (CH$_3$), 19.20 (CH$_3$), 24.80 (CH$_2$), 25.47 (CH$_3$), 29.40 (CH), 34.20 (CH$_2$), 35.99 (CH$_2$), 36.30 (CH$_2$), 124.44 (CH), 130.60 (C), 154.97 (CO).

A.2.1.10 Oxidation citronellyl urazole with DABCO-Br

0.66 g of citronellyl urazole (1 eq, 2.77 mmol) was solubilized in 20 ml dichloromethane (DCM) under inert atmosphere (N_2). 0.87 g DABCO-Br (0.2 eq, 0.55 mmol) was added to the mixture and stirred for 2 h at RT. The mixture was filtrated and the residu was

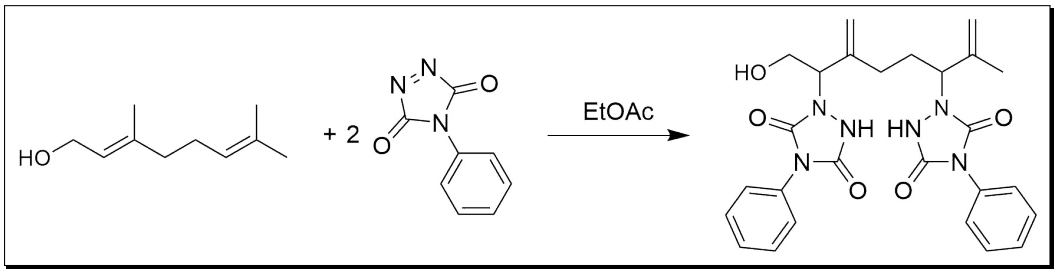
washed with 20 ml DCM. The filtrate was shortly concentrated *in vacuo*. The solution was further stirred overnight at RT, which turned from red to white the next morning. The product was concentrated *in vacuo*.

Molecular weight (DMA-SEC): 1010 g/mol

T_{deg} (TGA): 125 °C

A.2.2 Hyperbranched polymers

A.2.2.1 Alder-ene reaction between PhTAD and geraniol

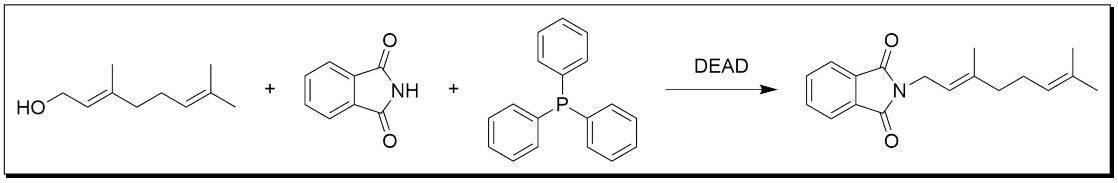


0.062 g Geraniol (1 eq, 0.4 mmol) was stirred in 0,6 mL EtOAc. Afterwards, 0.14 g PhTAD (2 eq, 0.8 mmol) was added. After 24 h stirring, the solution turned from red to light yellow. The solution was concentrated *in vacuo*.

Chemical formula: $C_{26}H_{28}N_6O_5$

Molecular weight: 504.55 g/mol

A.2.2.2 Synthesis of geranylphtalimide via the Mitsunobu reaction



A mixture of 11.02 g phthalimide (1 eq, 74.9 mmol), 19.6 g triphenylphosphine (1 eq, 74.9 mmol) and 11.5 g geraniol (1 eq, 74.9 mmol) in 50 mL dry THF was cooled to 0°C. 13.04 g diethyl azodicarboxylate (DEAD) (1 eq , 74.9 mmol) in 50 ml of dry THF was added dropwise over 30 minutes. The reaction mixture was then allowed to warm to RT and stirred overnight. The solvent was concentrated *in vacuo* and the residue suspended in Et_2O. The precipitate was filtered and the filtrate was concentrated *in vacuo*. Column

chromatography with EtOAc as eluens was performed. The product was obtained with a minor fraction of triphenylphosphine oxide.

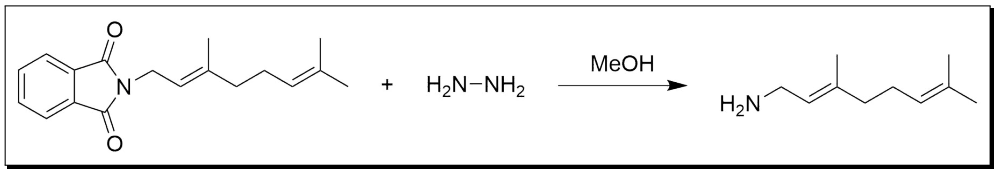
Yield: 101.8 %

Chemical formula: $C_{18}H_{21}NO_2$

Molecular weight: 283.37 g/mol

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.51 (s, 3 H, CH_3−C−CH_3), 1.56 (s, 3 H, CH_3−C−CH_3), 1.75 (s, 3 H, CH_3−C−CH_2), 1.99 (m, 4 H, CH_2−CH_2), 4.15 (d, 2 H, CH_2−N), 5.01 (t, 1 H, CH_2−CH=C), 5.19 (t, 1 H, N−CH_2−CH), 7.85 (m, 4 H, Ar−H).

A.2.2.3 Synthesis of geranylamine via the Mitsunobu reaction



A mixture of 21.6 g N-geranyl-phthalimide (1 eq, 76.2 mmol) and 5.57 mL hydrazine monohydrate (1.5 eq, 114.3 mmol) in 500 mL methanol was heated at reflux for 1 h and then concentrated *in vacuo*. The residue was dissolved in 250 mL 1M HCl and insoluble compounds were removed by filtration. The filtrate was made basic with 5M NaOH and extracted with Et_2O (3 x 250 mL). The combined ether layer was washed twice with saturated brine (2 x 100 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded geranylamine as orange/red liquid.

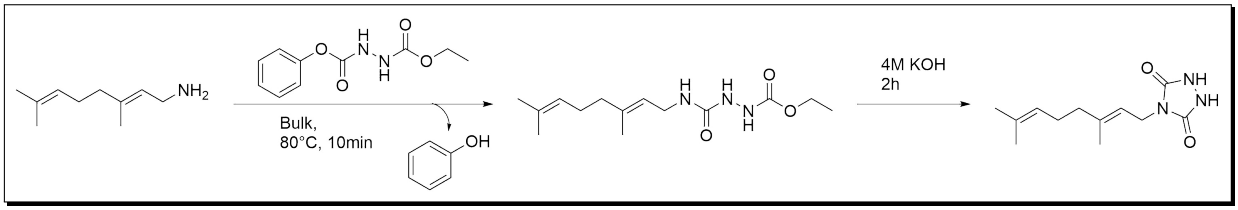
Yield: 67.6 %

Chemical formula: $C_{10}H_{19}N$

Molecular weight: 153.27 g/mol

^{1}H-NMR (400 MHz, DMSO−d_6): δ (ppm) = 1.38 (m, 2 H, NH_2), 1.56 (s, 6 H, CH_3−C−CH_3), 1.65 (s, 3 H, CH_3−C−CH_2), 1.94 (m, 2 H, CH_2−CH=C), 2.03 (m, 2 H, CH=C−CH_2), 3.11 (d, 2 H, NH_2−CH_2), 5.09 (t, 1 H, CH_2−CH_2−CH), 5.19 (t, 1 H, NH_2−CH_2−CH).

A.2.2.4 Synthesis of geranyl urazole



2.14 g EPHD (1 eq, 9.5 mmol) was melted at 80 °C under inert atmosphere (N_2). 1.46 g geranyl amine (1 eq, 9.5 mmol) was added and the mixture was stirred for 10 minutes. Column chromatography was performed with hexane:ethyl acetate (2:1) as eluens. Subsequently, 10 mL 4 M KOH was added to the reaction mixture and refluxed for 2 h. The mixture was cooled to RT and treated with 1 M HCl solution until pH=1 was reached. The precipitated was filtered off and dried under vacuum at 40 °C. The pure product was obtained.

Semicarbazide

Yield: 51 %

Chemical formula: $C_{14}H_{25}N_3O_3$

Molecular weight: 283.4 g/mol

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.17 (t, 3 H, O−CH_2−CH_3), 1.56 (s, 3 H, CH_3−C−CH_3), 1.61 (s, 3 H, CH_3−C−CH_3), 1.64 (s, 3 H, CH_3−C−CH_2), 1.93 (t, 2 H, $(CH_3)_2$−C−CH−CH_2), 2.02 (t, 2 H, $(CH_3)_2$−C−CH−CH_2−CH_2), 3.60 (t, 2 H, CH−CH_2−NH), 4.02 (q, 2 H, O−CH_2−CH_3), 5.08 (t, 1 H, $(CH_3)_2$−C−CH), 5.12 (t, 1 H, CH−CH_2−NH), 6.30 (s, 1 H, CH−CH_2−NH), 6.7-7.2 (m, 5 H, Ar−H), 7.64 (s, 1 H, O−CO−NH), 8.72 (s, 1 H, NH−NH−CO−NH), 9.33 (s, 1 H, PhOH).

Urazole

Yield: 53 %

Chemical formula: $C_{12}H_{19}N_3O_2$

Molecular weight: 237.3 g/mol

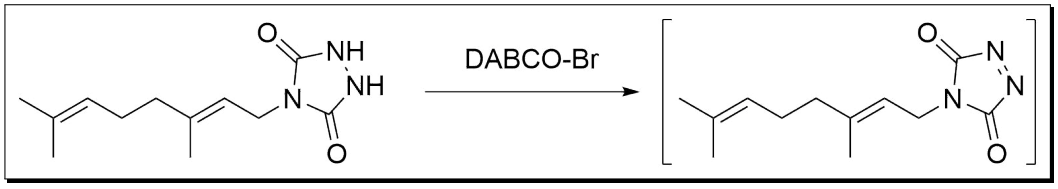
LC-MS (m/z): 238.1 $[MH]^+$

^{1}H-NMR (300 MHz, DMSO−d_6): δ (ppm) = 1.54 (s, 3 H, CH_3−C−CH_3), 1.62 (s,

3 H, CH_3−C−CH_3), 1.69 (s, 3 H, CH_3−C−CH_2), 1.97 (t, 2 H, $(CH_3)_2$−C−CH−CH_2), 2.01 (t, 2 H, $(CH_3)_2$−C−CH−CH_2−CH_2), 3.93 (d, 2 H, CH−CH_2−NH), 5.04 (t, 1 H, $(CH_3)_2$−C−CH), 5.12 (t, 1 H, CH−CH_2−NH), 10.00 (s, 2 H, NH−NH).

^{13}C-NMR (400 MHz, DMSO−d_6): δ (ppm) = 16.00 (CH_3), 17.53 (CH_3), 25.50 (CH_3), 25.83 (CH_2), 35.68 (CH_2), 38.78 (CH_2), 118.42 (CH), 123.83 (CH), 131.92 (C), 139.26 (C), 154.80 (CO).

A.2.2.5 Oxidation geranyl urazole with DABCO-Br



0.18 g of geranyl urazole (1 eq, 0.74 mmol) was solubilized in 20 mL dichloromethane (DCM) under inert atmosphere (N_2). 0.23 g DABCO-Br (0.2 eq, 0.014 mmol) was added to the mixture and stirred for 2 h at RT. The mixture was filtrated and the residu was washed with 20 ml DCM. The filtrate was shortly concentrated *in vacuo*. The solution was further stirred overnight at RT, which turned from red to white. The product was concentrated *in vacuo*.

Molecular weight (DMA-SEC): 1100 g/mol

T_{deg} (TGA): 160 °C

Appendix B

Materials

All products and solvents (Table B.1) were used as received without further purification.

Table B.1: Used products and solvents.

Name	CAS	Supplier	Purity (%)
Acetone	67-64-1	Sigma-Aldrich	99.8
Acetonitrile	75-05-8	Fisher Chemical	99.99
Allylamine	107-11-9	Sigma-Aldrich	99
6-Aminocaproic acid	60-32-2	Sigma-Aldrich	99
3-Amino-1-propanol	156-87-6	Sigma-Aldrich	99
Aniline	62-53-3	Sigma-Aldrich	99
Benzylamine	100-46-9	Sigma-Aldrich	99
Bromine	7726-95-6	Sigma-Aldrich	99
N-Bromosuccinimide	128-08-5	Sigma-Aldrich	98
Butylamine	109-73-9	Acros Organics	99
Chloroform-d	865-49-6	Euriso-Top	99.8
β-Citronellol	106-22-9	Sigma-Aldrich	95
Cyclohexanemethylamine	3218-02-8	TCI	98
Cysteamine	60-23-1	Sigma-Aldrich	95
1,8-Diazabicyclo(5.4.0)undec-7-ene	6674-22-2	Acros Organics	98
1,4-Diazabicyclo[2.2.2]octane	280-57-9	Sigma-Aldrich	99
Dichloromethane	75-09-2	Sigma-Aldrich	99.8
Diethyl ether	60-29-7	Sigma-Aldrich	99.8
Diethylazodicarboxylate, 40 wt% in toluene	1972-28-7	Sigma-Aldrich	-

Table B.1: Used products and solvents (continued).

Name	CAS	Supplier	Purity (%)
Dimethyl sulfoxide	67-68-5	Acros Organics	99.7
Dimethyl sulfoxide-d_6	2206-27-1	Euriso-Top	99.8
Diphenylcarbonate	102-09-0	Acros Organics	99
Ethanol	64-17-5	Sigma-Aldrich	99.8
Ethyl acetate	141-78-6	Sigma-Aldrich	99.7
Ethyl carbazate	4114-31-2	Sigma-Aldrich	97
Ethylenediamine	107-15-3	Acros Organics	99
Geraniol	106-24-1	Alfa Aeser	97
n-Hexane	110-54-3	Sigma-Aldrich	95
Hydrazine monohydrate	7803-57-8	VWR	98
Hydrochloric acid	7647-01-0	Chem-Lab	36
Hydrochloric acid, 5 to 6 N solution in 2-propanol	7647-01-0	Filter Service	-
Hydroquinone	123-31-9	Acros Organics	99
Isobutyric acid	79-31-2	VWR	99
Magnesium sulfate	7487-88-9	Boom	-
Methanol	67-56-1	Sigma-Aldrich	99.9
Octylamine	111-86-4	Sigma-Aldrich	99
Oleylamine	112-90-3	Sigma-Aldrich	98
Phthalimide	85-41-6	TCI	98
Potassium carbonate	584-08-7	Roth	99
Potassium hydroxide	1310-58-3	Sigma-Aldrich	90
Silica gel 60 Å	7631-86-9	Rocc	99.5
Sodium chloride	7647-14-5	Roth	99
Sodium hydroxide	1310-73-2	Acros Organics	97
Tetrahydrofuran	109-99-9	Sigma-Aldrich	99.9
Tetrahydrofurfurylamine	4795-29-3	TCI	98
Thionyl chloride	7719-09-7	Acros Organics	99.7
Toluene	108-88-3	Sigma-Aldrich	99.9
1,5,7-Triazabicyclo(4.4.0)dec-5-ene	5807-14-7	Sigma-Aldrich	98
Triphenylphosphine	603-35-0	Acros Organics	99

Appendix C

Equipment

Nuclear magnetic resonance

All ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker AVANCE 300 (300MHz) or a 400MHz AVANCE II Ultrashield Bruker. The obtained spectra were analysed with ACD/NMR Processor Academic Edition of ACD/Labs.

Liquid chromatography - mass spectrometry

LC-MS analyses were performed on an Agilent Technologies 1100 series LC/MSD system with a diode array detector (DAD) and single quad MS.

Differential scanning calorimetry

DSC analyses were performed with a Mettler Toledo instrument 1/700 under nitrogen atmosphere. In standard aluminium pans, 5 to 15 mg of the sample was weighed. Measurements were performed in a temperature range of -70 to 190 °C with a heating rate of 10 °C min^{-1}. The glass transition temperatures were determined from midpoints in the second heating scan using the STARe software of Mettler-Toledo.

Thermogravimetric analysis

TGA were performed on a Mettler Toledo TGA/SDTA 851e under nitrogen atmosphere. The sample was heated from 25 to 800 °C with a heating rate of 10 C min^{-1}. The thermograms were analyzed using the STARe software from Mettler-Toledo.

Fourier transform infrared

FT-IR with attenuated total reflection (ATR) were recorded on a Perkin Elmer FTIR SPECTRUM 1000 spectrometer and a PIKE Miracle ATR unit. For each sample, 16 scans were performed and the spectra were analyzed by IR software of Perkin Elmer.

Size exclusion chromatography

THF-SEC: All measurements were performed using a Varian PLGPC 50 plus instrument with a refractive index detector and two PLgel 5µm MIXED-D columns at 40 °C. For calibration, PMMA and PS were used and THF was the eluens with a flow rate of 1 mL min^{-1}. Samples were injected using a PL-AS RT autosampler.

DMA-SEC: All measurements were performed on a Agilent 1260-series HPLC system, which is equipped with a 1260 online degasser, a 1260 ISO-pump, a 1260 automatic liquid sampler (ALS), a thermastatted column compartment (TCC) at 50 °C equipped with a PSS Gram30 column in series with a PSS Gram1000 column, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). The used solvent was N,N-dimethylacetamide (DMA) containing 50 mM of LiBr with a flow rate of 1 mL/min. The spectra were analysed using the Agilent Chemstation software with the SEC add on. Molar mass and dispersity were calculated against Varian PMMA standards.

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