Screening the Synthesis of 2-Substituted-2-oxazolines

Kristian Kempe,[†,‡] Matthias Lobert,[†,§] Richard Hoogenboom,[†,§] and Ulrich S. Schubert*[,†,‡,§]

Laboratory of Macromolecular Chemistry and Nanoscience, Eindhoven University of Technology, Den Dolech 2, 5600 MB Eindhoven, The Netherlands, Laboratory of Organic and Macromolecular Chemistry, Friedrich-Schiller-University Jena, Humboldtstraβe 10, 07743 Jena, Germany, and Dutch Polymer Institute, P.O. Box 513, 5600 MB Eindhoven, The Netherlands

Received October 25, 2008

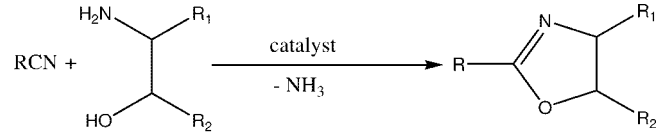
2-Oxazolines are well-known organic compounds which are included in a variety of complex biologically active structures and play a role as catalyst ligands and intermediates for functional compounds. In addition, 2-oxazolines serve as monomers for the synthesis of substituted poly(imine)s by cationic ring-opening polymerization. For the latter application, the feasibility of preparing new 2-substituted-2-oxazolines was investigated using an automated synthesizer. The reaction of various nitriles with 2-aminoethanol under Lewis acid catalysis was utilized for this purpose. Twenty-nine different substituted nitriles were selected out of more than 2000 commercial available nitriles to form the corresponding 2-oxazolines. At first, the reaction conditions were optimized for seven nitriles with regard to solvent and catalyst, including reproducibility tests in an automated parallel robot system. In the next step, the synthesis of all 29 2-oxazolines was screened in an automated parallel manner, whereby the reactions were monitored by GC-MS measurements providing novel insights in the scope of this synthesis route. These insights resulting from the high-throughput screening were validated by performing representative larger-scale syntheses of selected 2-oxazolines.

Introduction

The great importance of 2-oxazolines is based on their presence in a number of biologically active compounds,[1−3] as well as on their application as intermediates for functional structures.[4−6] In addition, 2-oxazolines are excellent catalyst ligands,[7−9] protecting groups,[10] and monomers for the cationic ring-opening polymerization (CROP).[11−15] A large number of methods for the synthesis of 2-substituted-2-oxazolines are known to date. Nitriles,[16] carboxylic acids,[10,17,18] and their derivatives, like esters[19,20] or acyl benzotriazoles,[21] are the main starting substrates. Moreover, the conversion of an alcohol or an aldehyde with molecular iodine or pyridinium hypobromide perbromide results in the formation of 2-oxazolines.[22,23] Recently Jordan et al. reported the synthesis of an 2-oxazoline starting from an already existing 2-oxazoline via nucleophilic attack to a organohalogene compound.[24] The reaction via the nitrile, which was first described by Witte and Seeliger in 1974, represents a simple one-pot reaction, where a nitrile is converted to the corresponding 2-oxazoline by reaction with an amino alcohol in the presence of a Lewis-acid catalyst (Scheme 1). The large commercial availability of a wide range of nitriles makes this reaction an ideal method to prepare a large number of new 2-oxazolines.

With respect to structure−property relationships of polymers, it is of great interest to prepare diverse 2-substituted-2-oxazolines because the 2-substituent forms the side chain of the resulting polymer and, thus, influences the properties as was demonstrated, for example, for poly(2-*n*-alkyl-2-oxazoline)s.[25] The potential synthesis of other substituted 2-oxazolines offers the possibility toward the preparation of new functional polymers and expands the base for the future design of new polymers with predictable properties. To be able to screen the synthesis of a large variety of 2-oxazolines, a high-throughput experimentation (HTE) approach was used. In the last decades, combinatorial and high throughput methods have been established in the pharmaceutical research.[26,27] The fast performance of parallel and simultaneous reactions on one side and the possibility for a fast monitoring on the other side made these techniques also highly interesting for the synthesis of organic and inorganic materials, catalysts, and polymers.[28−31] However, to fully exploit the possibilities of automation, it should be combined with design of experiments (DoE), which allows a significant

Scheme 1. Schematic Representation of the General Procedure for the Synthesis of 2-Substituted 2-Oxazolines via Nitriles



R_1, R_2 = H, Alkyl, Aryl ...

* To whom correspondence should be addressed. Fax: +49 3641 948 202; E-mail: ulrich.schubert@uni-jena.de.
† Eindhoven University of Technology.
‡ Friedrich-Schiller-University Jena.
§ Dutch Polymer Institute (DPI).

10.1021/cc800174d CCC: $40.75
Published on Web 02/23/2009

reduction of the required practical experiments without compromising the scientific insights.[32,33]

In this paper, we investigate the synthesis of new 2-oxazolines via the reaction of nitriles with 2-aminoethanol using a HTE approach. Therefore, a number of nitriles were selected from more than 2000 commercially available nitriles. The condensation reaction was optimized using seven of the selected nitriles with regard to solvent and catalyst. The resulting optimal conditions were applied to screen the 2-oxazoline synthesis for all the selected nitriles allowing the determination of the scope of this synthesis method. Finally, the resulting insights into the 2-oxazoline synthesis from nitriles were validated by preparing some of the 2-oxazolines in a larger scale.

Experimental Section

Materials and Instrumentation. Various nitriles were purchased from Aldrich, AcrosOrganics, and Apollo. 2-aminoethanol, zinc acetate, and chlorobenzene were obtained from Aldrich, and 1-butanol was obtained from Biosolve Ltd. All chemicals were used without further purification.

The screening was carried out on a Chemspeed ASW2000 automated synthesizer. The reactions were performed utilizing a reactor block with 16 reaction vessels of 13 mL. The reaction vessels were equipped with a common heating jacket, which was connected to a Huber Unistat Tango device (−40 to 145 °C) and with coldfinger reflux condensers that could be cooled or heated from −5 to 50 °C. An inert atmosphere was maintained by applying a 1 bar argon flow over the reactors. The reaction mixtures were analyzed with a Shimadzu GCMS-QP5050A; the mass values are reported as mass/charge ratios (*m*/*z*). All spectra were measured with a column temperature program from 80 to 300 °C (25 K/min) and 3 min hold time at 300 °C. The injection temperature was set to 300 °C, and the detector temperature was set to 250 °C. Gas chromatography (GC) was measured on an Interscience Trace gas chromatograph with a Trace Column RTX-5 connected to a PAL autosampler. ^{1}H NMR and ^{13}C NMR spectra of the products were recorded on a Varian Mercury 400 spectrometer at room temperature in $CDCl_3$ or MeOH-d_4 as solvent. The chemical shifts are given in parts per million (ppm) relative to residual nondeuterated solvent signals. IR spectra were measured on a Perkin-Elmer 1600 FT-IR spectrometer.

Oxazoline Screening. The reactants were utilized in the following ratios of nitrile:2-aminoethanol:catalyst 1:1.2:0.025. The reaction mixture possessed a nitrile concentration of 2 M and a volume of 5 mL. First, the catalyst (zinc acetate or cadmium acetate) was manually weighed into the reaction vessels. The amount of the solvent (chlorobenzene or 1-butanol) and the nitrile were added automatically, and the reaction vessels were heated to 130 (chlorobenzene) and 120 °C (1-butanol), respectively. Finally, the appropriate amount of 2-aminoethanol was added to the reaction mixture. An argon flow was applied over the reaction vessels to remove the formed ammonia. After reaction times of 2.5, 5, 7.5, 10, 14, 18, and 24 h, 50 μL samples were transferred from the reaction vessels to GC vials containing 1 mL of chloroform. Cooling of the reaction mixture stopped the reaction after 24 h. The amount of product was calculated by the determination of the ratio of the integral of the desired product peak to all integrals of the measured peaks in the GC-MS spectrum.

General Procedure for the 2-Oxazoline Synthesis. The nitrile (1 equiv) and zinc acetate (catalyst; 0.02 equiv) were heated to 130 °C without solvent. After the addition of 2-aminoethanol (1.2 equiv), the resulting suspension was stirred at 130 °C and monitored by GC-MS. When the reaction was completed, the reaction mixture was cooled to ambient temperature, and $CHCl_3$ was added. The organic phase was washed 3 times with water and 1 time with brine and dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by further distillation or column chromatography.

2-(4-(Trifluoromethylthio)phenyl)-2-oxazoline (M14). The oxazoline was purified by column chromatography (SiO_2, dichloromethane:ethylacetate 4:1, 1% NEt_3). Yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.98 (d, 2H, ^3J (3-H, 4-H) = 8 Hz, 3-H), 7.69 (d, 2H, ^3J (4-H, 3-H) = 8 Hz, 4-H), 4.45 (t, 2H, ^3J (2-H, 1-H) = 9.6 Hz, 2-H), 4.08 (t, 2H, ^3J (1-H, 2-H) = 9.6 Hz, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): 163.58 (C-8), 135.78, 130.88, 130.03, 129.04, 127.71 (C-3−C-7), 67.87 (C-2), 55.07 (C-1). GC-MS retention time: 6.43 (100%, M^+ = 247). Elemental analysis: calcd, C 48.58 H 3.26 N 5.67 S. 12.97; exptl, C 48.77 H 3.55 N 5.42 S 12.60.

2-(1-(4-Chlorophenyl)cyclobutyl)-2-oxazoline (M9). The crude product was purified by column chromatography (Al_2O_3, dichloromethane:ethylacetate 4:1, 1% NEt_3). Yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.26 (m, 4H, 6-H, 7-H), 4.21 (t, 2H, ^3J (2-H, 1-H) = 9.6 Hz, 2-H), 4.85 (t, 2H, ^3J (1-H, 2-H) = 9.6 Hz, 1-H), 2.8 (m, 2H, 3-H/5-H), 2.48 (m, 2H, 3-H/5-H), 2.12 (m, 1H, 4-H/4′-H), 1.88 (m, 1H, 4-H/4′-H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.59 (C-11), 143.2 (C-8), 132.3 (C-9), 128.33 (C-7), 127.69 (C-6), 68.07 (C-2), 54.39 (C-1), 32.53 (C-3, C-5), 16.75 (C-4). GC-MS retention time: 7.98 (100%, M^+ = 235). Elemental analysis: calcd, C 66.24 H 5.99 N. 5.94; exptl, C 66.11 H 6.03 N 6.33.

Results and Discussion

2-Oxazoline Screening. Twenty-nine different substituted nitriles were selected leading to a large variety of 2-oxazolines, including alkyl-substituted nitriles, several fluorine-containing nitriles, nitriles with ether and thioether bonds, and acetal and phosphonate functions (Figure 1). This range of functionalities was chosen to provide information about the principle accessibility of a diverse range of potentially interesting 2-substituted-2-oxazolines for the cationic ring-opening polymerization. The reaction between the corresponding nitrile and 2-aminoethanol under Lewis-acid catalysis was used for the synthesis. This reaction is perfectly suited for utilizing an automated synthesis robot because only one component, the nitrile, has to be changed. Furthermore, it allows a simple successive addition of all substances and sampling after definite times. The goal of this high-throughput screening was to obtain an overview of the feasibility of these syntheses. In addition, we intended to

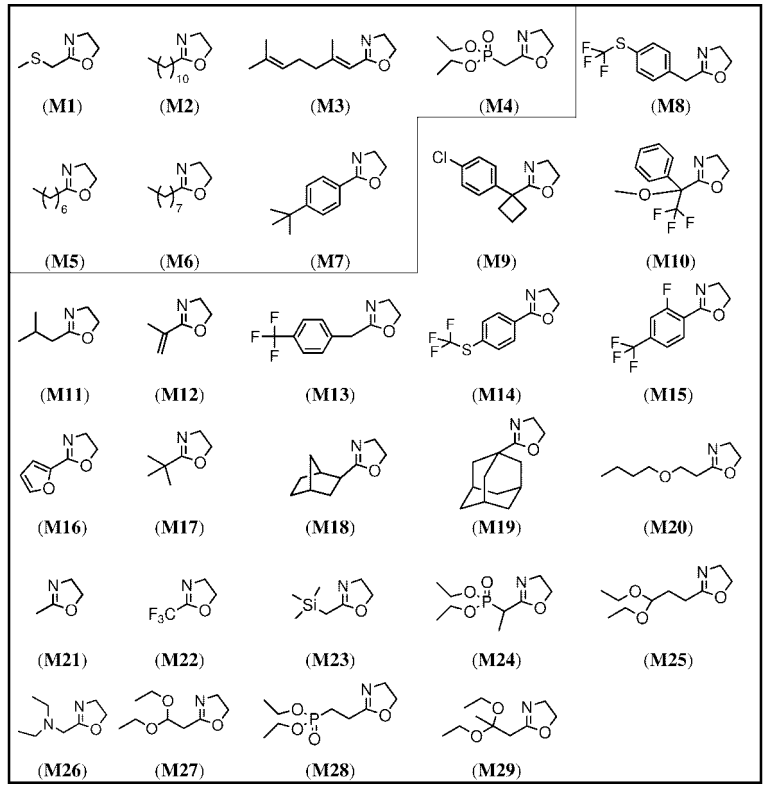


Figure 1. Schematic representation of the selected 2-oxazolines prepared starting from the corresponding nitriles. The 2-oxazolines in the highlighted area were used for the optimization of the reaction conditions.

identify the optimal reaction conditions; therefore different catalysts and solvents were tested. Reaction conditions including solvent were chosen to have a broadly applicable screening procedure for both liquid and solid nitriles. On the basis of the results of these investigations, the synthesis procedures should be directly transferrable into larger laboratory scale synthesis with or without solvent.

The screening of the 2-oxazoline synthesis was performed utilizing an ASW2000 synthesis robot from Chemspeed Technologies with one reactor block allowing the parallel screening of 16 reactions. The starting molar ratios, temperature, solvents, and reagents were chosen according to a literature procedure.[16] In every single reactor, the solid catalyst was manually weighed in first. All other components were added automatically. The reactions mixture was heated to 130 °C, and after 2.5, 5, 7.5, 10, 14, 18 and 24 h, 50 μL samples were taken for GC-MS analysis to identify the products and side products, as well as to generate a kinetic plot for every reaction.

At first, the optimization of the nitrile 2-aminoethanol condensation reaction was performed with seven of the selected nitriles by changing the solvent from chlorobenzene to 1-butanol and by changing the catalyst from zinc acetate to cadmium acetate resulting in the formation of the following 2-oxazolines: 2-((methylthio)methyl)-2-oxazoline (**M1**), 2-undecyl-2-oxazoline (**M2**), 2,6-dimethylhepta-1,5-dienyl-2-oxazoline (**M3**), 2-diethylmethylphosphonate-2-oxazoline (**M4**), 2-octyl-2-oxazoline (**M5**), 2-heptyl-2-oxazoline (**M6**), and 2-(4-*tert*-butylphenyl)-2-oxazoline (**M7**). Because of technical restrictions, namely, a blockage of the needles through the resulting viscose reaction mixture during the sampling for GC-MS, the investigation of a theoretically imaginable bulk reaction was not included in our research.

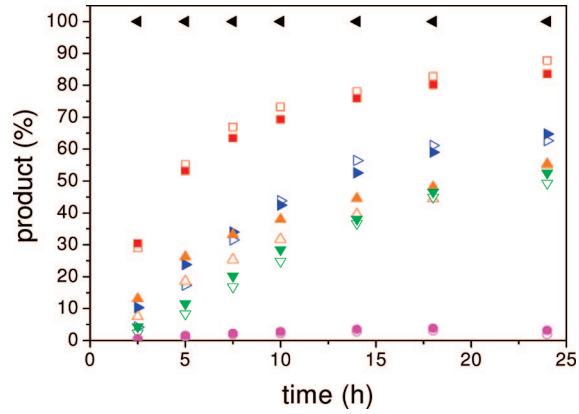


Figure 2. Results of the reproducibility tests in the robot using chlorobenzene and zinc acetate. All reactions were performed twice (filled and unfilled symbols), and the final product amounts were determined by GC-MS measurements (black symbol, **M1**; red symbol, **M7**; blue symbol, **M5**; orange symbol, **M2**; green symbol, **M6**; magenta symbol, **M3**).

In regard to reproducibility tests of the robot, the synthesis in chlorobenzene as solvent and $Zn(OAc)_2$ as catalyst was performed twice, and the corresponding GC-MS samples were measured subsequently. The graphs of conversion in time provide a good indication for the reproducibility of the syntheses performed in the robot (Figure 2). All syntheses that led to the desired 2-oxazoline only revealed small deviations, for both, syntheses with high conversion (**M1**), as well as those with low conversion (**M3**). The effect of the substituent on the synthesis of the oxazolines will be discussed later.

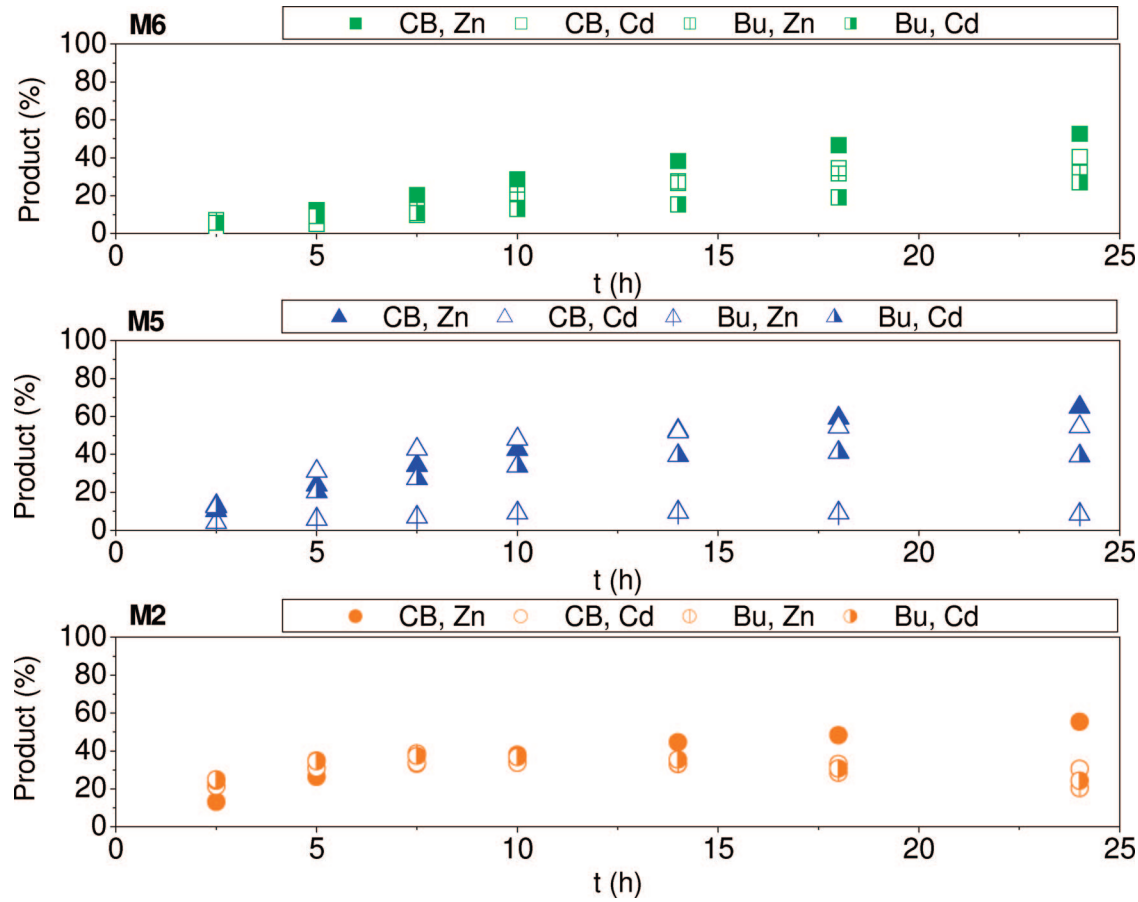


Figure 3. Kinetic plots for the synthesis of 2-alkyl-substituted-2-oxazolines (**M2**, **M5**, and **M6**) using different solvents (CB = chlorobenzene; Bu = 1-butanol) and catalysts (Zn = zinc acetate; Cd = cadmium acetate).

Since we were able to prove the general feasibility of the applied reaction setup by means of the reproducible conversion data, the reaction conditions were optimized subsequently. Therefore the seven selected nitriles were reacted with 2-aminoethanol using cadmium acetate as catalyst. Two more runs were performed to monitor the reaction in 1-butanol as solvent, with zinc acetate on the one hand and cadmium acetate on the other hand. For the reactions in 1-butanol, one had to decrease the temperature to 120 °C because of the boiling point of the solvent. (It should be taken into account that the amount of product after 24 h could be influenced by the lower temperature resulting in lower conversion of the nitrile compared to the reactions in chlorobenzene at 130 °C.) The kinetic plots that demonstrate the formation of product with respect to the reaction time are depicted in Figures 3 and 4. The synthesis starting from the diethyl cyanomethyl-phosphonate did not led to the desired oxazoline **M4**, and therefore, it is not included into the graphs. Instead of the formation of the 2-oxazoline, another product was identified via GC-MS. One can assume that a substitution of the phosphonate residue through the 2-aminoethanol has occurred because the obtained product could be identified as *N,N*-diethyl-2-aminoethanol with a molar mass of 117 g/mol.

For the synthesis of 2-alkyl-2-oxazolines, chlorobenzene seems to be the most suitable solvent. Independent from the catalyst we obtained in all cases the highest amounts of products in this solvent. In addition, zinc acetate is a better catalyst for the reaction in chlorobenzene than cadmium acetate. In general, zinc acetate results in higher or at least the same product percentages compared to cadmium acetate, which makes it a better catalyst for these kinds of substituted 2-oxazolines. Changing the substituent in 2-position revealed changes in the optimal conditions for the reaction. The synthesis of **M3** was found to be optimal using 1-butanol as solvent, whereas the combination of chlorobenzene/cadmium acetate and chlorobenzene/zinc acetate led to the highest amount of product for the 2-alkyl-2-oxazolines. The small difference in the values for the different catalysts is negligible. The marginal product amount of the latter synthesis is caused by the formation of four products showing the same molar mass. Because of the two double bonds in this nitrile, we assume that four stereoisomers were formed. The values in Table 1 refer to the peak with the highest intensity. The formation of **M1** is the fastest synthesis included in this optimization. Already after 2.5 h, we observed full conversion independent of the reaction conditions.

In conclusion, reaction conditions including the solvent chlorobenzene and zinc acetate at 130 °C were identified to provide the best yields and were subsequently applied for the synthesis of the remaining 2-oxazolines. Even if the synthesis of **M3** shows a higher product percentage using cadmium as catalyst and 1-butanol as solvent the reaction in chlorobenzene provides information about the feasibility of this reaction and could be used for further investigations.

The selected 29 syntheses included some more diverse 2-alkyl-2-oxazolines. However, the kinetic studies of **M11**,

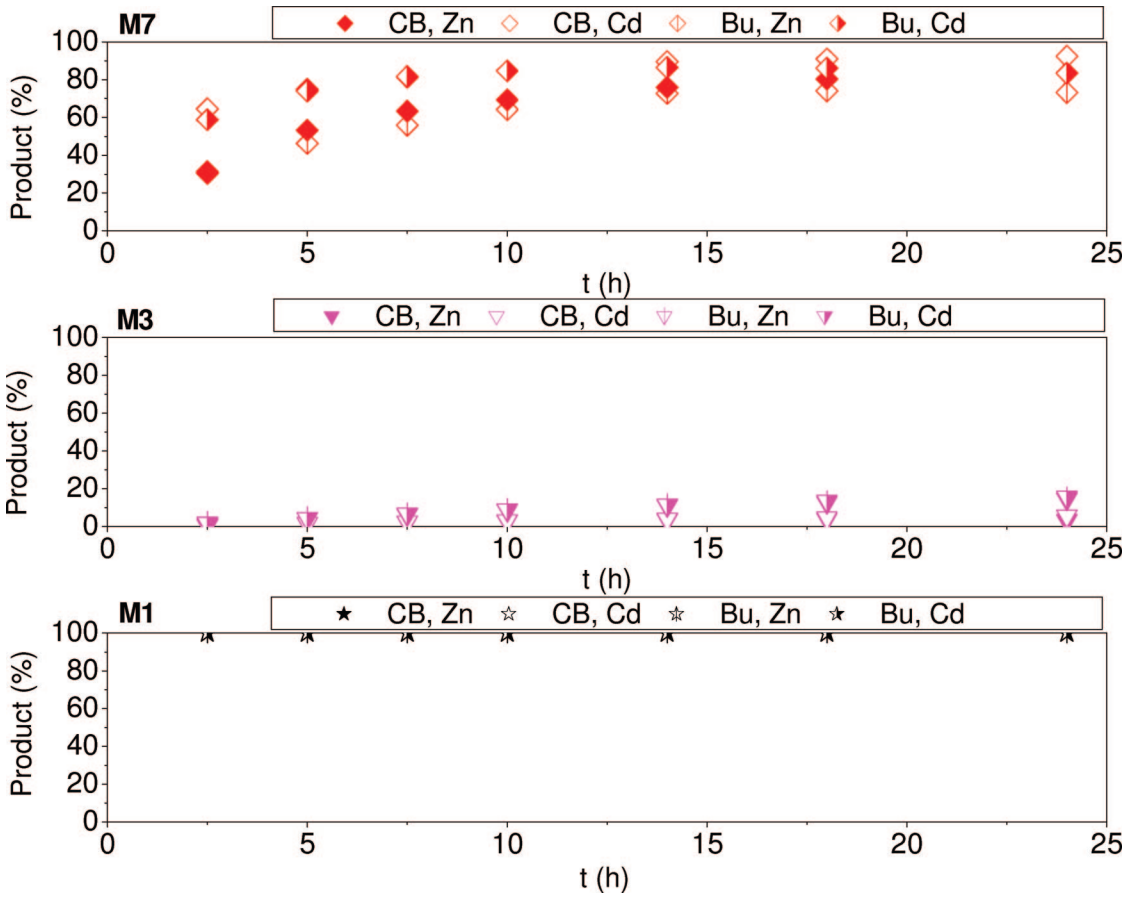


Figure 4. Kinetic plots for the synthesis of the other substituted 2-oxazolines included in the optimization process (**M1**, **M3**, and **M7**) using different solvents (CB = chlorobenzene; Bu = 1-butanol) and catalysts (Zn = zinc acetate; Cd = cadmium acetate).

Table 1. Results of the Optimization Experiments[a]

	product (%) after 24 h			
2-oxazoline	Zn, CB	Cd, CB	Zn, Bu	Cd, Bu
M1	100	100	100	100
M2	55	31	20	24
M3	3	6	15	16
M5	65	55	8	39
M6	52	40	32	27
M7	88	92	73	83

[a] Zn = zinc acetate; Cd = cadmium acetate; CB = chlorobenzene; Bu = 1-butanol.

M12, and **M17** were not conclusive because the boiling points of the starting materials, as well as of the products are lower than the reaction temperature of 130 °C, resulting in a loss of substance. Nonetheless, the syntheses of these three monomers via the nitrile route are possible as some product formation was observed. Figure 5 and Table 2 provide an overview of the kinetic screening of the remaining monomers as well as a total overview of the formed products for all 29 nitriles, respectively. Nitriles containing trifluoromethyl- or trifluoromethylthio-groups bound to an aromatic ring resulted in the formation of the desired 2-oxazolines. An extra fluorine atom on the aromatic ring leads to a side reaction, caused by a nucleophilic attack of 2-aminoethanol, resulting in the substitution of the fluorine atom.[34] According to this, the reaction of 2-fluoro,4-trifluoromethyl-phenylnitrile with 2-aminoethanol results in the formation of a small amount of the desired 2-oxazoline **M15** in addition to the substituted nitrile and 2-oxazoline. The syntheses of **M1** and

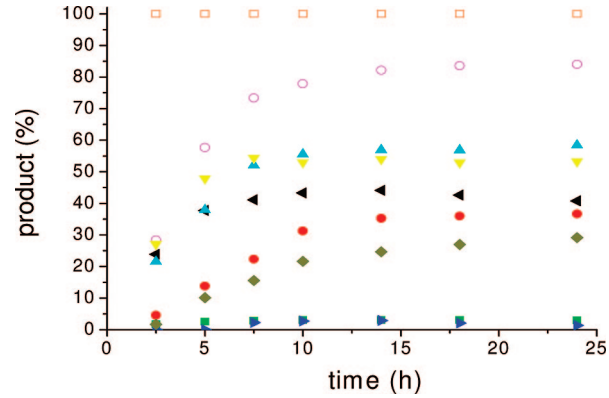


Figure 5. Product vs time plots for the successfully synthesized 2-oxazolines ($Zn(Oac)_2$; chlorobenzene; 130 °C) (orange symbol, **M16**; magenta symbol, **M14**; aqua symbol, **M8**; yellow symbol, **M13**; black symbol, **M20**; red symbol, **M10**; olive green symbol, **M9**; green symbol, **M15**; blue symbol, **M18**).

M16 occur with remarkably short reaction times. These fast reactions showed, after 2.5 h, almost no existence of the educt in the GC-MS spectra; with proceeding reaction time only the formation of larger amounts of the ring-opened version was observed. Another interesting 2-oxazoline could be the successfully prepared 2-oxazoline **M9** because of its sterically demanding cyclobutane ring and the chloro-functionalization. In addition, it was possible to synthesize the more complex 2-oxazolines **M18** and **M19**. The product peaks in the GC-MS spectra indicate the possibility of using this synthetic route. Further investigations on these reactions in larger scale

Table 2. Overview of the Screening Results[a]

oxazoline	percent	oxazoline	percent	oxazoline	percent	oxazoline	percent	oxazoline	percent
M1	100	**M2**	55	**M3**	16	**M4**	0	**M5**	65
M6	52	**M7**	88	**M8**	58	**M9**	29	**M10**	20
M11	nd	**M12**	nd	**M13**	53	**M14**	84	**M15**	5
M16	100	**M17**	nd	**M18**	2	**M19**	1	**M20**	41
M21	nd	**M22**	nd	**M23**	0	**M24**	0	**M25**	0
M26	0	**M27**	0	**M28**	0	**M29**	0		

[a] Product amount after 24 h, calculated by GC-MS. nd = not determined.

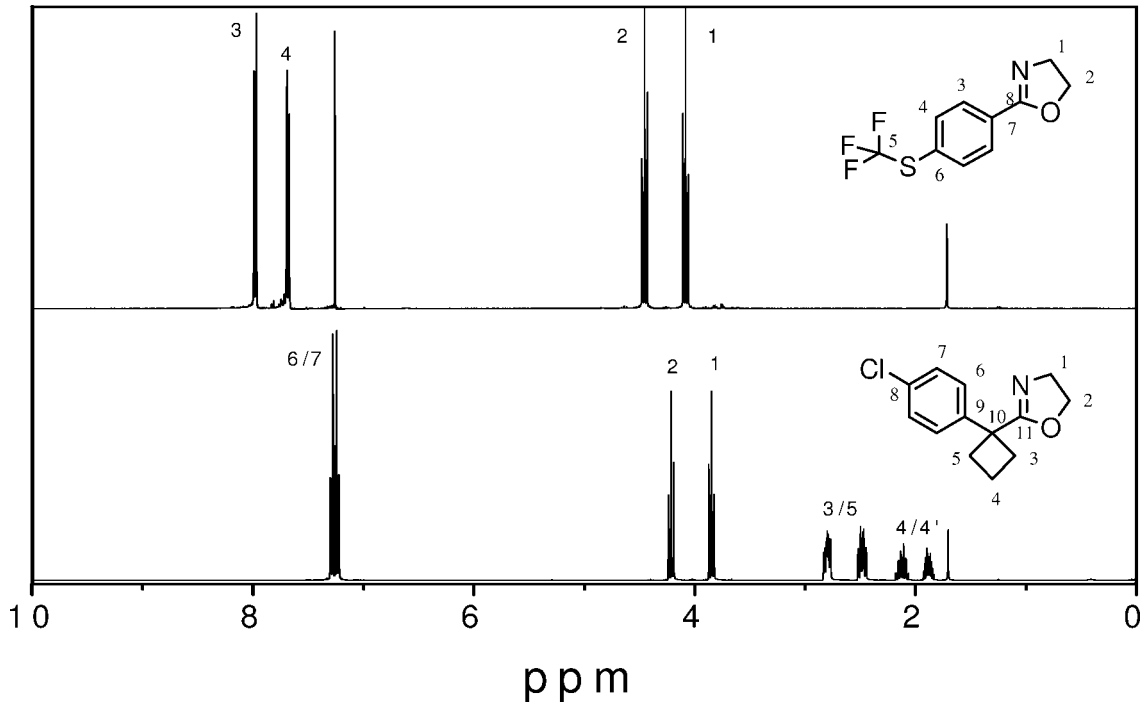


Figure 6. ^{1}H NMR spectra of **M14** (top) and **M9** (bottom) in $CDCl_3$.

revealed the increase of the conversion up to 60%. In addition to the described 18 successful prepared 2-oxazolines, only a few nitriles showed no product formation in the GC-MS spectra. In total only eight 2-oxazolines could not be synthesized using this synthetic route because the 2-oxazolines **M21** and **M22** were not included in this screening because of their low boiling points. Nitriles bearing an acetale- and phosphonate-group in 2-position showed side reactions that prevented the formation of the desired 2-oxazolines. In addition to its nucleophilic character, 2-aminoethanol could act as a base which probably effects a cleavage of the phosphonate-groups and a hydrolysis of the acetal-functions. By means of the GC-MS measurements *N,N*-diethyl-2-aminoethanol could be identified as the main side product obtained in the synthesis of phosphonat-containing 2-oxazolines. Furthermore, GC-MS delivers a hint for another phosphorus containing side product, which was proven by ^{31}P NMR but could not be identified in detail.

Laboratory Syntheses. By preparing selected 2-oxazolines on a larger scale, the significance of the robot syntheses should be proven before the obtained knowledge concerning the feasibility of the syntheses can be generally transferred to the laboratory. In contrast to the robot syntheses, we omitted the solvent for liquid nitriles to accelerate the synthesis. The catalyst was added to neat nitrile, and the suspension was heated to 130 °C before adding 2-aminoethanol. Followed by a washing procedure, the crude product was purified by distillation or column chromatography depending on the state (liquid or solid) of the product. The obtained 2-oxazolines were characterized using ^{1}H and ^{13}C NMR spectroscopy, as well as GC-MS and elemental analysis.

Compounds **M14** and **M9** were prepared starting from 10 g of the corresponding nitrile. The first synthesis was stopped after 7 h reaction time by the addition of chloroform, whereas the second synthesis took 22 h as monitored by GC-MS. Both crude products were purified by column chromatography (SiO_2; CH_2Cl_2/ethyl acetate 4:1), whereby the synthesis of **M14** resulted in a yield of 59% and **M9** in 49% yield, respectively. Figure 6 displays the ^{1}H NMR spectra of the obtained 2-oxazolines. The proton peaks of the oxazoline ring appear in both cases between 4 and 4.9 ppm showing triplets for both CH_2 groups, which is a clear indication for the formation of the 2-oxazoline ring structure. These successful syntheses clearly demonstrate that the screening provides significant results for the scope of the nitrile 2-aminoethanol condensation to substituted 2-oxazolines.

Conclusions

In conclusion, the successful preparation of 18 2-oxazolines utilizing an automated parallel synthesizer could be shown. On the basis of reproducibility tests and optimization

steps, zinc acetate as catalyst and chlorobenzene as solvent were found to represent the optimal conditions for the reaction between the nitrile and 2-aminoethanol. Utilizing the results of the screening, we successfully synthesized two 2-oxazolines in the laboratory, which indicates the possibility for a direct transfer of the feasibility results to laboratory experiments. The interpretation of these results, as well as the polymerization of these monomers, using theoretical models is currently under progress.

Acknowledgment. The authors thank the Dutch Polymer Institute (DPI) and the Fonds der Chemischen Industrie for financial support.

References and Notes

(1) Ishihara, M.; Togo, H. *Synlett.* **2006**, 227–230.
(2) Genet, J. P.; Thorimbert, S.; Touzin, A. M. *Tetrahedron Lett.* **1993**, *34*, 1159–1162.
(3) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Synlett.* **2005**, 2747–2750.
(4) Lee, Y. J.; Lee, J. Y.; Kim, M. J.; Kim, T. S.; Park, H. G.; Jew, S. S. *Org. Lett.* **2005**, *7*, 1557–1560.
(5) Hatano, M.; Asai, T.; Ishihara, K. *Chem. Lett.* **2006**, *35*, 172–173.
(6) Seijas, J. A.; Vazquez-Tato, M. P.; Martinez, M. M.; Pizzolatti, M. G. *Tetrahedron Lett.* **2005**, *46*, 5827–5830.
(7) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organomet.* **1989**, *8*, 846–848.
(8) Nishiyama, H.; Park, S. B.; Itoh, K. *Tetrahedron: Asymmetry* **1992**, *3*, 1029–1034.
(9) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325–2328.
(10) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353–9372.
(11) Kobayashi, S.; Uyama, H. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 192–209.
(12) Aoi, K.; Okada, M. *Prog. Polym. Sci.* **1996**, *21*, 151–208.
(13) Hoogenboom, R.; Schubert, U. S. *Green Chem.* **2006**, *8*, 895–899.
(14) Hoogenboom, R. *Macromol. Chem. Phys.* **2007**, *208*, 18–25.
(15) Wiesbrock, F.; Hoogenboom, R.; Leenen, M. A. M.; Meier, M. A. R.; Schubert, U. S. *Macromolecules* **2005**, *38*, 5025–5034.
(16) Witte, H.; Seeliger, W. *Liebigs Ann. Chem.* **1974**, 996–1009.
(17) Whelligan, D. K.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 4609–4618.
(18) Kangani, C. O.; Kelley, D. E.; Day, B. W. *Tetrahedron Lett.* **2006**, *47*, 6497–6499.
(19) Hughey, J. L.; Knapp, S.; Schugar, H. *Synthesis* **1980**, 489–490.
(20) Aidouni, A.; Demonceau, A.; Delaude, L. *Synlett* **2006**, 493–495.
(21) Katritzky, A. R.; Cai, C. M.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004**, *69*, 811–814.
(22) Sayama, S. *Synlett* **2006**, 1479–1484.
(23) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474–1480.
(24) Taubmann, C.; Luxenhofer, R.; Cesana, S.; Jordan, R. *Macromol. Biosci.* **2005**, *5*, 603–612.
(25) Hoogenboom, R.; Fijten, M. W. M.; Thijs, H. M. L.; Van Lankvelt, B. M.; Schubert, U. S. *Des. Monomers Polym.* **2005**, *8*, 659–671.
(26) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472.
(27) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144–154.
(28) Hoogenboom, R.; Fijten, M. W. M.; Schroer, J.; Schubert, U. S. *Macromol. Rapid Commun.* **2003**, *24*, 98–103.
(29) Hoogenboom, R.; Fijten, M. W. M.; Meier, M. A. R.; Schubert, U. S. *Macromol. Rapid Commun.* **2003**, *24*, 92–97.
(30) Hoogenboom, R.; Fijten, M. W. M.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 1830–1840.
(31) Hoogenboom, R.; Wiesbrock, F.; Leenen, M. A. M.; Meier, M. A. R.; Schubert, U. S. *J. Comb. Chem.* **2005**, *7*, 10–13.
(32) Adams, N.; Schubert, U. S. *J. Comb. Chem.* **2004**, *6*, 12–23.
(33) Adams, N.; Schubert, U. S. *Macromol. Rapid Commun.* **2004**, *25*, 48–58.
(34) Lobert, M.; Kohn, U.; Hoogenboom, R.; Schubert, U. S. *Chem. Commun.* **2008**, 1458–1460.

CC800174D