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High-Temperature Diels−Alder Reactions: Transfer from Batch to Continuous Mode

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Supporting Information

ABSTRACT: The transfer of a Diels−Alder reaction of (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **1** with α-acetoxyacrylonitrile **2** and acrylonitrile **8**, respectively, from batch to continuous mode is presented, using standard and widely available laboratory equipment. A standard microwave-based system was used as probe for the transfer to flow reactors. Temperature and residence time have been optimized in small coiled-tube reactors and confirmed with two production runs in a flow reactor. The inherent increase in safety caused by the small volumes at high temperatures and the achieved productivity (approximately 100 g/h using acrylonitrile) are offering advantages over the batch mode which suffers from thermokinetic limitations for scale-up.

INTRODUCTION

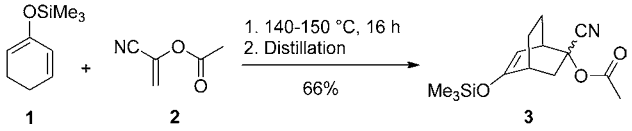
The scale-up of [4 + 2] Diels−Alder cycloadditions is a challenge in view of the inherent instability of the diene and/or dienophile, especially for highly reactive reagents.[1] Competing side reactions such as rapid, uncontrolled polymerization with explosive violence are a safety issue[2] which must be addressed early on when any scale-up is considered. In the course of our research towards a scalable access to a key building block for an active pharmaceutical ingredient (API) at Actelion,[1,3] such safety risks associated with the Diels−Alder reaction of α-acetoxyacrylonitrile **2** or α-chloroacrylonitrile as dienophiles and (cyclohexa-1,5-dien-1-yloxy)trimethylsilane as diene **1** have been thoroughly assessed with reaction calorimetry (RC-1) and isothermal DSC experiments.[4] This culminated in the design and development of an efficient and safe process securing the timely delivery of 450 kg of intermediate emerging from the Diels−Alder reaction with α-chloroacrylonitrile in batch mode.[1] However, the use of α-acetoxyacrylonitrile (**2**) was restricted to a few kilograms on the basis of these safety studies.[4] We thus turned to an alternative dienophile, acrylonitrile **8**, which offered, in addition, the possibility of running the Diels−Alder reaction in a solvent.[1]

To cope with the restrictions imposed by the exothermic full batch mode with both α-acetoxyacrylonitrile and acrylonitrile, we reckoned that this cycloaddition process would be well-suited for a continuous mode. This should, in addition, provide a contingency technology for the timely supply of intermediates. From the outset, we set ourselves the challenge to employ conventional lab equipment that could be used for a straightforward, low-cost, and easy-to-implement flow reactor setup.[5]

HIGH TEMPERATURE DIELS−ALDER REACTION WITH α-ACETOXYACRYLONTIRILE

First, the Diels−Alder reaction of diene **1** with α-acetoxyacrylonitrile **2** was tested. This reaction was usually carried out in full batch mode (neat) at a temperature of 140−150 °C over 16 h, affording, after distillation, the cyclo-adduct **3** in 66% yield on kilogram scale (Scheme 1).[1] Safety studies of this reaction indicated a maximum temperature of the synthesis reaction (MTSR) of 250 °C, at which temperature decomposition would set in immediately with an increase in temperature to 429 °C.[4] Clearly, this reaction was not scalable to larger volumes.

Scheme 1. Diels−Alder reaction of diene 1 with α-acetoxyacrylonitrile 2 in batch mode; only the main regioisomer is shown, consisting of a mixture of both diastereoisomers (endo/exo)



To get an insight for the kinetics of this reaction, an equimolar mixture of diene **1** and dienophile **2** was stirred in a glass bottle at 140 °C for 24 h. Figure 1 shows the conversion of diene **1** as a function of time.[6] The NMR assay of the reaction mixture was determined to be 67% w/w; however, no byproducts were detected by ^{1}H NMR. This led to the assumption that a considerable part of the reagents (especially the diene **1**) had polymerized during the reaction (polymers being difficult to detect by NMR or GC). This polymer formation might cause problems when transferring this reaction into a microreactor system by blocking its fine structures.

A first test in continuous mode was done in a coaxial heat exchanger module from Ehrfeld.[7] The reactants were premixed before being fed to the microreactor and a simple manual

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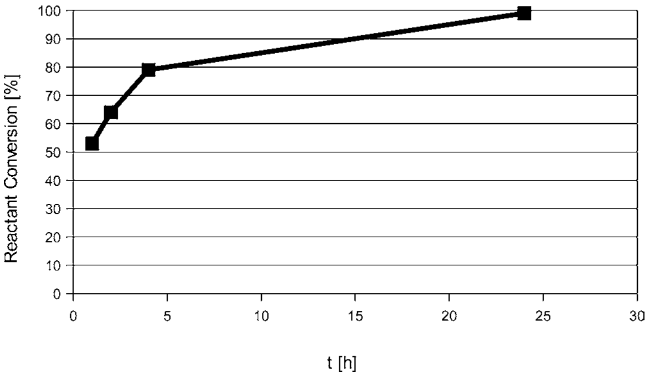


Figure 1. Conversion[6] of diene **1** as a function of time in the Diels−Alder reaction of **1** and **2** in neat batch mode at 140 °C.

pressure valve from Swagelok was used to increase the pressure in the system.[8] The temperature limit for this system was 195 °C which proved to be too low to get short residence times; only about 20% conversion was observed at 2-min residence time. In order to heat to higher temperature, the reactor setup was then modified to a simple coiled steel tube that was put into a liquid metal bath[9] as shown in Figure 2.

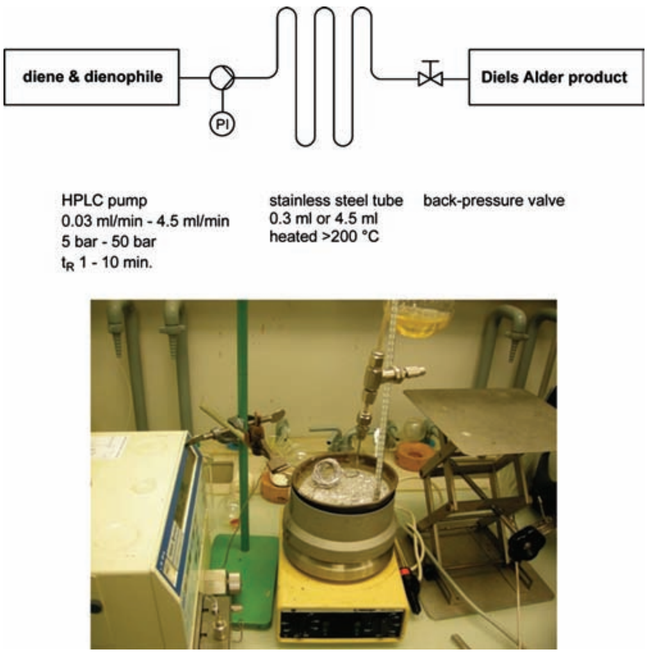


Figure 2. Simple flow reactor setup using a Rose metal bath as heating source and a Swagelok pressure valve (see the Experimental Section for the detailed parameters of the flow reactors).

The metal bath allowed for reaction temperatures of up to 300 °C. With this new setup a temperature/conversion screening was done (Figure 3).

Higher temperatures led to higher conversion; however, more undesired byproducts were concomitantly formed, as judged by ^{1}H NMR analysis of the crude reaction mixture. The diene **1** proved to be unstable and formed several byproducts. The most prominent ones were identified and assigned by two-dimensional (2D) NMR spectra (COSY and HSCQ) (Figure 4).

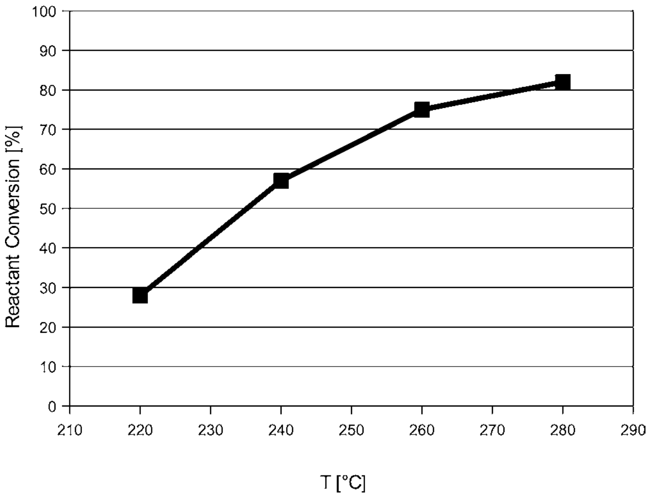


Figure 3. Reactant conversion[6] of diene **1** in the Diels−Alder reaction of **1** and **2** after 1 min at different temperatures in the flow mode.

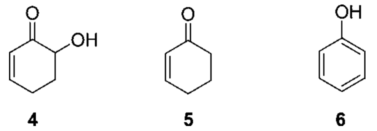


Figure 4. Byproducts formed in the Diels−Alder reaction of **1** and **2** at high temperatures without exclusion of oxygen.

It was found that the hydroxylated enone **4** was formed via a Rubottom reaction when keeping the crude reaction mixture at rt under an atmosphere of air for several hours. The impurities, 2-cyclohexenenone (**5**) and phenol (**6**), were formed in increasing amounts when the reaction mixture was passed through the flow reactor at higher temperatures. The influence of the stainless steel tubing on decomposition reaction at this high temperature[10] was not studied—we did not observe any change in the impurity profile over time, using our equipment. A typical ^{1}H NMR spectrum of a crude product is shown in Figure 5, with assignment of the impurities **4**, **5**, and **6**.

Next, we tested whether it was possible to optimize the productivity with minimal byproduct formation. Therefore, several residence times were screened at 250 °C, a temperature at which byproduct formation seemed reasonably low as observed by NMR of the crude material. Starting with an equimolar mixture of **1** and **2**, the reaction mixture contained some unreacted diene **1** after 2.5 min, whereas **1** had completely disappeared after 5 and 10 min. The ratio of dienophile **2** and product **3** was stable after 5 min, but the amount of byproduct (especially enone **5**) increased at longer residence times (Figure 6). This is in agreement with the finding that the impurities **5** and **6** are formed at higher reaction temperature.

In order to reduce the amounts of byproduct **5** and **6**, which were assumed to be derived from an acid-catalyzed removal of the TMS-protection group from diene **1**, the reaction mixture was saturated with a non-nucleophilic base (Na_2CO_3). This led to the formation of gas bubbles at the outlet as well as to the formation of a new series of aromatic byproducts (reaction temperature 250 °C, residence time 5 min). One of these could be identified as 4-cyanophenol (**7**). Scheme 2 shows a possible mechanism for the formation of this new byproduct that would be associated with the formation of ethylene gas (Alder−Rickert reaction).[11] The other source of a gas could be CO_2 from the decomposition of Na_2CO_3.

When diluting the reaction mixture with an equal amount of toluene, a significant decrease of the reaction rate was observed, and the same byproducts were formed. To accelerate the neat

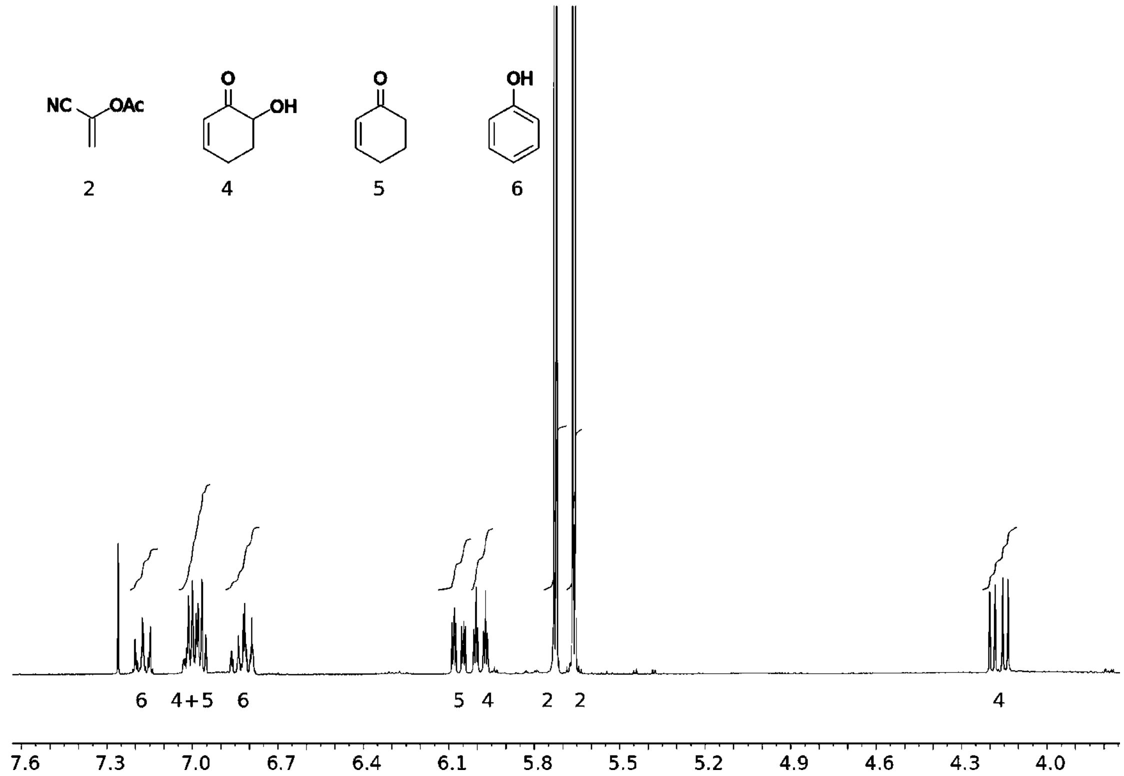


Figure 5. Byproducts formed from a mixture of diene **1** and α-acetoxyacrylonitrile **2** after keeping the mixture at 175 °C for 2 min and then at rt for 100 h. ^{1}H NMR in $CDCl_3$.

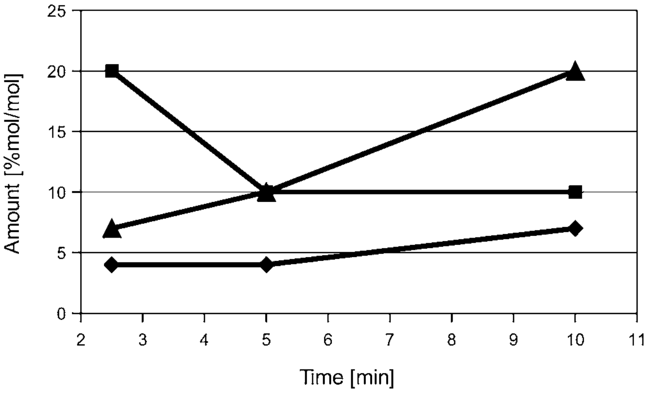


Figure 6. Amounts of byproduct formed in the Diels–Alder reaction of equimolar amounts of **1** and **2** at 250 °C. Molar ratios of **2** (■), **5** (▲) and **6** (◆) are presented relative to the amounts of product **3** formed at the same time, according to ^{1}H NMR (mol %).

Scheme 2. Possible mechanism for the formation of 4-cyanophenol 7 via an Alder–Rickert reaction in the presence of Na_2CO_3

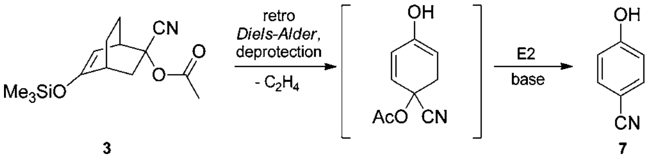
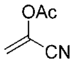
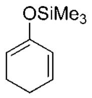
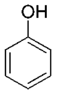
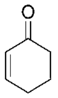


Table 1. Byproducts formed in the Diels–Alder reaction of 1 and 2 (1.5 equiv 1) at 250 °C[a]

time [min]				
	2	**1**	**6**	**5**
2.5	310%	450%	traces	traces
5	7%	51%	13%	10%

[a]Values are relative to the amounts of product **3** formed at the same time according to ^{1}H NMR (mol %).

Diels–Alder reaction, 1.5 equiv of the diene **1** were used next.[12] The results for two different residence times at 250 °C in the flow reactor are shown in Table 1. Accordingly, the dienophile **2** reacted faster while less of cyclohexenone **5** was formed.

The best compromise between long residence times at low temperatures on the one hand and byproduct formation at higher temperatures on the other hand was finally the reaction of 1.5 equiv of diene **1** with dienophile **2** at 250 °C and a residence time of 10 min. In a production experiment, the small flow reactor (Experimental Section) was operated under these conditions for 1.75 h after conditioning, i.e. running the reactor steadily with the process parameters. During that time no clogging of the reactor was observed, and the pressure in the reactor was constant at 5 bar. The crude product's content was 44% w/w (^{1}H NMR assay, see Experimental Section), which corresponds to an assay-corrected yield of 57% (Table 2). The ^{1}H NMR of the crude product indicated the typical impurities described above. The risks associated with this Diels–Alder reaction have been mitigated by the transfer from batch to continuous mode. However, the dienophile **2** was not commercially available because its custom synthesis required handling

Table 2. Overview of the parameters for the Diels–Alder reactions of diene 1 with dienophiles 2 and 8

dienophile	α-acetoxyacrylonitrile **2**[a]	acrylonitrile **8**[b]
ratio of **1**:dienophile	1.5:1	1:3
reaction temp	250 °C	215 °C
residence time	600 s	60 s
assay-corrected yield	57%	65%
isolated yield	–	33%[d]
productivity	11 g/h[c]	96 g/h[c]/48 g/h[d]

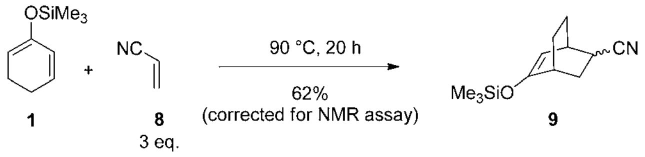
[a] Data from the 'small flow reactor' (0.03 mL, 0.3 mL/min, 5 bar), used in this work. [b] Data from the 'large flow reactor' (4.5 mL, flow rate 4.5 mL/min, 50 bar), used in this work. [c] Based on assay-corrected yield (by ^{1}H NMR) of crude reaction mixture. [d] Based on isolated yield after distillation.

of cyanides, and it was not stable enough for large-scale manufacturing.[1,4]

HIGH TEMPERATURE DIELS–ALDER REACTION WITH ACRYLONITRILE

Acrylonitrile (**8**) is much cheaper and less toxic[13] than α-acetoxyacrylonitrile **2**. Therefore, an excess of this dienophile was deemed acceptable and should have a positive effect on the kinetics of the bimolecular reaction to the desired Diels–Alder product **9**. Again, the batch reaction served as starting point (Scheme 3). Diene **1** and 3 equiv of acrylonitrile **8** were heated in an oil bath set at 90 °C for 20 h. The yield of cycloadduct **9** was 62% after correction for the NMR assay of the crude reaction mixture. Nitrile **9** was formed as an endo/exo mixture of regioisomers with the depicted 2,5-isomer as main product. The distillation was thwarted by polymerization of acrylonitrile. Later,[1] we found 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO) as a suitable polymerization inhibitor for the system of **1** and acrylonitrile **8**. The addition of catalytic amounts of TEMPO prevented the polymer formation during the Diels–Alder reaction with excess acrylonitrile in neat batch conditions and enabled isolation of **9** by distillation (Experimental Section, 62% corrected yield). Likewise, an equimolar mixture of diene **1** and acrylonitrile was reacted in xylenes at 135 °C jacket temperature for 16 h. The nitrile **9** was isolated in 65% yield after distillation.[14] Still, the exothermic neat full-batch mode of this reaction triggered the development of a flow reactor technology.

Scheme 3. Neat Diels–Alder reaction of diene 1 with acrylonitrile 8 as dienophile in batch mode



In preliminary batch experiments polymerization of acrylonitrile was observed. To avoid any problem in continuous processing by blocking the channels of microreactors, the reaction was therefore screened first in a microwave reactor at different temperatures.[15] A microwave reactor is perfectly suited for higher temperature under pressure. A 1:1 mixture of diene **1** and acrylonitrile **8** was heated for 2 h at different temperatures. The reaction mixture was analyzed by ^{1}H NMR, and the molar amounts of starting materials **1** and **8** left relative to that of product **9** were determined (Figure 7). The impurities **4**, **5**, and **6** were not observed mainly due to the lower temperature as compared to those of reactions with dienophile **1** (250 °C). The amount of both starting materials left in the crude reaction mixture decreased with increasing reaction temperature. It was also observed (not shown) that a temperature of at least ~175 °C is required to attain a reasonable reaction rate for the Diels–Alder reaction. As the amount of unreacted acrylonitrile was always significantly lower than that for diene **1**, we assumed that polymerization of acrylonitrile took place as a side reaction. We therefore decided to use an excess of acrylonitrile which should simultaneously accelerate the Diels–Alder reaction.

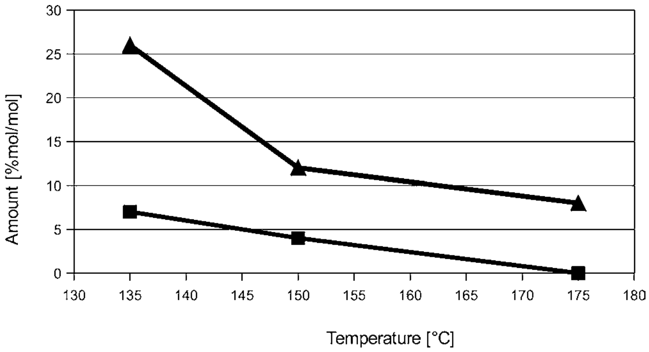


Figure 7. Screening of the temperature of the Diels–Alder reaction of diene **1** and acrylonitrile **8** at a ratio of 1:1 for 2 h. Molar ratios of **1** (▲) and **8** (■) are presented relative to the amounts of product **9** formed at the same time, according to ^{1}H NMR (mol %).

By applying the van't Hoff rule as approximation—an increase of the reaction temperature by 10 °C results in a doubling of the reaction rate—we raised the reaction temperature by 30 °C to 205 °C, which should reduce the residence time of 2 h by a factor of 8 to ~10 min. In the following, a residence time screening was done in the flow reactor at 205 °C using 1.2 equiv of acrylonitrile (Figure 8). The diene **1** was consumed within 5 min, whereas some acrylonitrile **8** was still detected in the crude reaction mixture.

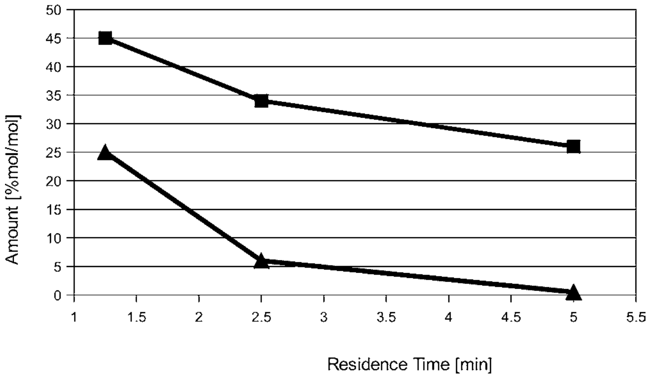


Figure 8. Screening of the residence time of the Diels–Alder reaction of diene **1** and acrylonitrile **8** at a ratio of 1:1.2 at 205 °C. Molar ratios of **1** (▲) and **8** (■) are presented relative to the amount of product **9** formed at the same time, according to ^{1}H NMR (mol %).

With 2 equiv of acrylonitrile and a reaction temperature of 205 °C, the diene was already consumed after 1.25 min. A residence time of ~1 min secured a reasonable productivity for continuous processing. No precipitation was observed in the reaction mixture during or after the reaction. An increase of the amount of acrylonitrile to 3 equiv and of the temperature to 215 °C allowed for an acceptable residence time of ~1 min (Figure 9). The yield of Diels–Alder product **9** was 81%, corrected for the NMR assay of the crude reaction mixture (56% w/w).

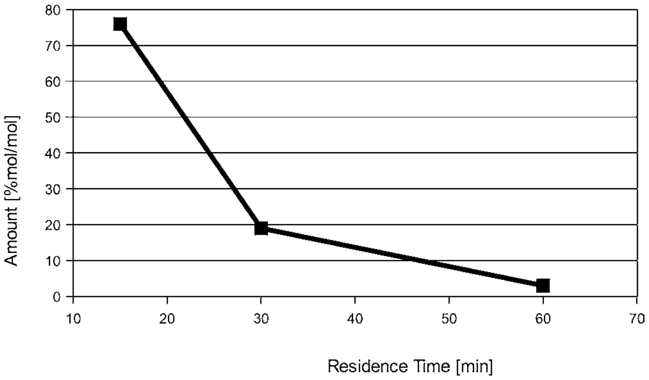


Figure 9. Residence time screening of the Diels–Alder reaction of diene **1** and acrylonitrile **8** at a ratio of 1:3 at 215 °C. Molar ratios of **1** (■) are presented relative to the amounts of product **9** formed at the same time, according to ^{1}H NMR (mol %).

These final conditions (i.e., 3 equiv acrylonitrile, 215 °C, 1 min) were then confirmed in two production runs. First, the 0.3 mL flow reactor (‘small flow reactor’) was operated for 35 min at 215 °C with a residence time of 60 s. The assay-corrected yield was 56%. In a second experiment, a larger steel tube with an inner diameter of ~2 mm and a volume of 4.5 mL was used (‘large flow reactor’, Table 2). During 45 min, 164 g of reaction mixture was collected and purified by vacuum distillation. The purity of the reaction mixture was acceptable for downstream chemistry (44% w/w by NMR assay, 65% assay-corrected yield).[16]

With these flow parameters at hand, the requirements for a productivity of 100 kg Diels–Alder products **3** or **9** in 24 h were estimated for a flow reactor with internal diameter of 4 mm (Table 3). While the reaction with α-acetoxyacrylonitrile **2** would require a coil with 132-m length, a 31-m tube with a flow rate of ~23 L/h would be sufficient for the production of 100 kg of **9** from acrylonitrile **8** and diene **1**.

Table 3. [a] **Estimated mass and flow reactor requirements for a production of 100 kg 3 or 9 in 24 h, extrapolated with flow parameters of the two production runs in Table 2**

	α-acetoxyacrylonitrile **2**	acrylonitrile **8**
	72 kg	218 kg
diene **1**	164 kg	230 kg
flow reactor volume	1665 mL	390 mL
flow reactor length	132 m	31 m
flow reactor internal diameter	4 mm	4 mm
flow rate	10.0 L/h	23.4 L/h

[a] Based on assay-corrected yield (by ^{1}H NMR) of crude reaction mixture.

■ CONCLUSIONS

High-temperature Diels–Alder reactions of (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **1** and α-acetoxyacrylonitrile **2** or acrylonitrile **8** have been transferred from batch to continuous mode. Microwave heating was successfully used for the screening of the temperature and optimal residence time. A key feature is the use of a simple steel tube and a Swagelok pressure valve for this flow reactor system. Although it was possible to reach a practical reaction time of 10 min for the Diels–Alder reaction of α-acetoxyacrylonitrile **2** with 1.5 equiv of diene **1** by increasing the temperature to 250 °C, this led to the formation of several new byproducts and polymerization. The reaction of diene **1** with acrylonitrile **8** has been transferred into a continuous process at 215 °C with a residence time of ~1 min by using a large excess of this dienophile (3 equiv). The crude yield was comparable to the one obtained in the batch reaction. The formation of polymeric byproduct from acrylonitrile during distillation of the Diels–Alder product **9** was omitted by the addition of an inhibitor (TEMPO) to the reaction mixture.[17] A short-path distillation for continuous product isolation would be the preferred option on larger scales.

■ EXPERIMENTAL SECTION

General. All chemicals were reagent grade and used as supplied, unless stated otherwise. Analytical thin layer chromatography (TLC): precoated *Merck* silica gel 60 F254 plates (0.25 mm). Column chromatography (FC): *Fluka* silica gel 60 (230–400 mesh). ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a *Bruker AVANCE 300*. Chemical shifts (δ) are reported in ppm relative to Me_4Si (0.00 ppm). NMR assay: the content (% w/w) of all crude products and reaction mixtures was assessed by NMR assay with dihydroquinone dimethylether as internal standard. In case of bicycle **3**, integrals of the signals of the bridgehead hydrogen C(1)H (two dt at 3.3–3.2 ppm) were compared to the integral of the methyl singlet of dihydroquinone dimethylether (3.56 ppm). In case of bicycle **9** the olefin signals (two dd at 5.2–5.0 ppm) were used as the reference signal. In all cases, the time between scans (relaxation delay, D1) was set to 20 s. Microwave equipment: reactions under microwave irradiation were carried out in a closed vessel in a *Biotage Initiator* device. Flow reactor setup: (a) *Small flow reactor*: coiled stainless steel tube (0.3 mL, 680-mm length, 0.75-mm I.D.). (b) *Large flow reactor*: coiled stainless steel tube (4.5 mL, 1200-mm length, 2.2-mm I.D.). For heating, the reactors were immersed in a metal bath (Rose’s alloy: 50% Bi, 25% Pb, 25% Sn). The feed was pumped using a Merck Hitachi L-6200A HPLC pump with a pressure control (a *Swagelok SS* needle valve).

Synthesis of *rac*-2-Cyano-5-(trimethylsilyloxy)bicyclo[2.2.2]oct-5-en-2-yl acetate (3). *Reference Batch Experiment.* A mixture of diene **1** (9.21 g, 54.8 mmol, 1 equiv) and α-acetoxyacrylonitrile (**2**) (6.09 g, 54.8 mmol, 1 equiv) was stirred at 140 °C for 24 h. The amount of product was determined by ^{1}H NMR assay at regular intervals. After 24 h, 99% of the dienophile **2** has reacted and crude **3** was obtained as thick, brown oil. Yield: 15.3 g (100% uncorrected yield). NMR-assay: 67% w/w. This corresponds to an assay-corrected yield of 67%.

Production Run, Small Flow Reactor. The feed—prepared by mixing diene **1** (5.04 g, 5.60 mL, 30 mmol, 1.5 equiv) and α-acetoxyacrylonitrile (**2**) (2.22 g, 2.09 mL, 20 mmol, 1 equiv)—was pumped with a flow of 0.03 mL/min (this corresponds to a residence time of 10 min) through the small flow reactor at 250 °C and a pressure of 5 bar. The reactor was run under these conditions for 15 min before the reaction mixture was collected during 1.75 h to afford crude **3** as brown oil. Yield: 3.1 g (104% recovery, 8.2 mmol **2**). NMR assay: 44% w/w. This corresponds to an assay-corrected yield of 57%.

Analytical data of byproduct.[18] 6-Hydroxy-2-cyclohexenone (**4**). ^{1}H NMR ($CDCl_3$):[19] δ 6.98 (br, dt, J = 10.1, 4.1 Hz, 1H); 5.98 (dt, J = 10.1, 2.0 Hz, 1H); 4.14 (dd, J = 13.7, 5.6 Hz, 1H); 2.7−1.8 (m, 4H). These values are in accordance with literature values.[20]

2-Cyclohexenone (**5**). ^{1}H NMR ($CDCl_3$): 7.0 (m, 1H); 6.07 (dt, J = 10.0, ~2.0 Hz, 1H); 2.7−1.8 (m, 6H). These values are in accordance with literature values.[21]

Phenol (**6**). ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 2H), 6.87−6.78 (m, 3H).

Synthesis of *rac*-5-(Trimethylsilyloxy)bicyclo[2.2.2]oct-5-ene-2-carbonitrile (9). *Batch Reaction (without TEMPO, in Xylenes).* TMS−diene **1** (50 g, 0.297 mol, 1 equiv) and acrylonitrile (**8**) (19.5 mL, 0.297 mol, 1 equiv) were dissolved in xylenes (100 mL) and heated to 135 °C (oil bath) at normal pressure for 16 h. The solvent was removed under reduced pressure. Distillation under high vacuum (~0.1 mbar) and a head temperature of 95 °C afforded **9** as a colorless liquid. Yield: 43 g (65% uncorrected).

Batch Reaction (Neat, with Tempo). TMS−diene **1** (50 g, 0.297 mol, 1 equiv), TEMPO (0.5 g, 0.003 mol, 0.01 equiv) and acrylonitrile (**8**) (58.7 mL, 0.891 mol, 3 equiv) were heated to 90 °C (external temperature) for 24 h. Distillation under high vacuum (~0.1 mbar) and a head temperature of 90 °C afforded **9** as a colorless liquid. Yield: 55 g (84% uncorrected). NMR assay: 74% w/w. This corresponds to an assay-corrected yield of 62%.

Batch Reaction (Neat, without Tempo). TMS−diene **1** (50 g, 0.297 mol, 1 equiv) and acrylonitrile (**8**) (58.7 mL, 0.891 mol, 3 equiv) were heated to 90 °C (external temperature) for 20 h. The mixture was cooled to 20 °C to obtain **9** as a yellow, viscous oil. Yield: 97 g (62% corrected by assay by ^{1}H NMR ($CDCl_3$): 42% w/w). Distillation at 88−95 °C head temperature, 130 °C bath temperature, and ~0.1 mbar afforded purified **9** as a colorless liquid. Yield: 30 g (46% uncorrected). NMR assay: 85% w/w. This corresponds to an assay-corrected yield of 39%.

Production Run, Small Flow Reactor. The feed—prepared by mixing diene **1** (8.4 g, 9.33 mL, 50 mmol, 1 equiv) and acrylonitrile (**8**) (7.96 g, 9.83 mL, 150 mmol, 3 equiv)—was pumped with a flow of 0.3 mL/min (this corresponds a residence time of 60 s) through the small flow reactor at 215 °C and a pressure of 50 bar. The reactor was run under these conditions for 10 min before the reaction mixture was collected for 35 min to afford crude **9** (8.926 g, 100% recovery, 27.3 mmol **1**). The excess acrylonitrile was evaporated under reduced pressure (40 °C, 20 mbar) affording **9** as a brown turbid oil. Yield: 6.046 g (100% uncorrected). Only traces of impurities were detected in the ^{1}H and ^{13}C NMR spectra. NMR assay: 56% w/w. This corresponds to an assay-corrected yield of 56%.

Production Run, Large Flow Reactor. The feed, prepared by mixing diene **1** (117.7 g, 130.8 mL, 0.7 mol, 1 equiv) and acrylonitrile (**8**) (111.4 g, 137.5 mL, 2.1 mol, 3 equiv), was pumped with a flow of 4.5 mL/min (this corresponds to a residence time of 60 s) through the large flow reactor at 215 °C and a pressure of 50 bar. The reactor was operated under these conditions for 2 min before the reaction mixture was collected for 45 min to afford crude **9** (164 g, 95% recovery, 0.5 mol **1**). NMR assay of crude reaction mixture: 44% w/w. This corresponds to an assay-corrected yield of 65%. Vacuum distillation (bath temperature: 150 °C, head temperature 90 °C, 0.1 mbar) afforded **9** as colorless oil. Yield: 36.4 g (33%). Due to polymerization (viscous liquid) some product was left trapped in the distillation flask. NMR data correspond to those of **9**.[1]

ASSOCIATED CONTENT

Supporting Information

GC−MS method, representatives copies of ^{1}H NMR of compounds **3** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Determined by comparing the olefin signals of the diene **1** at 5.7 ppm with the bridgehead signals of the Diels−Alder product **3** at 3.25 ppm; conversion is defined as the percentage of the integral of **3** to the sum of the integrals of **1** and **3**.

(7) The www.ehrfeld.com web site (accessed 12 May 2011).

(8) Microreactor setup: Ehrfeld coaxial heat exchanger (0.62 mL) heated with a Julabo ME-6 thermostate, Merck Hitachi L-6200A HPLC pump system, Swagelok needle valve

(9) (a) Rose's alloy: 50% Bi, 25% Pb, and 25% Sn with a melting point of 98 °C. (b) Electrical heating is the preferred option for heating for larger production systems.

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(12) An excess of the diene **1** was used, since the dienophile **2** is more toxic and less readily available.

(13) Acrylonitrile is a bulk chemical, is readily available on large scale, and has fewer toxicity issues as compared to **2** as no cyanides in the waste stream have to be treated in the downstream chemistry.[1]

(14) Forsyth et al. used 2.5 equiv acrylonitrile in toluene at 140 °C for 24 h, 92% undistilled crude yield, see: Forsyth, D. A.; Botkin, J. H.; Puckace, J. S.; Servis, K. L.; Domenick, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 7270−7276.

(15) Applied for the Diels–Alder reaction of acrylonitrile and 2,3-dimethylbutadiene, see ref 5d.

(16) Only 33% of the product **9** was isolated after distillation. This was due to polymerized acrylonitrile in the crude reaction mixture, which led to difficulties during the distillation process, see ref 17.

(17) Successfully demonstrated in batch mode where contact times are longer as compared to continuous mode (Experimental Section).

(18) Based on ^{1}H NMR spectra of a mixture of compounds **2**, **4**, **5**, and **6**. Some of the signals could therefore only be roughly assigned.

(19) The signal of the OH group was hidden under the signals of other compounds and could not be assigned.

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