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A Two-Step Continuous-Flow Synthesis of *N*-(2-Aminoethyl)acylamides through Ring-Opening/Hydrogenation of Oxazolines

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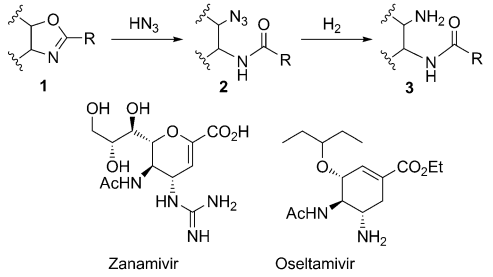
2-Oxazolines are a readily available class of heterocycles that are easily generated from aminoalcohols and carboxylic acids, or through alternative synthetic procedures starting from alkenes or epoxides as substrates.[1,2] The oxazoline moiety is very resistant against a range of reagents, such as nucleophiles, bases, or radicals, and is, therefore, heavily used as protecting and/or directing group, or as a powerful source of chirality in asymmetric synthesis.[1–3] Under acidic conditions, however, oxazolines are susceptible to nucleophilic ring-opening. Thus, the S_N2 attack of a nucleophile at the ether carbon C5 of the ring leads to β-substituted carboxamides as products.[1,2,4–7] This reaction is extensively employed in glycoside synthesis, whereby an anomeric oxazoline is used as the glycopyranosyl donor.[1,2,4]

Importantly, the ring-opening of oxazolines with an azide source is a key step in the synthesis of neuraminic acid analogues (e.g., neuraminidase inhibitors, such as Zanamivir and Oseltamivir) and may attain equal importance for the preparation of other pharmaceutically active compounds that contain the *N*-(2-aminoethyl)acylamide scaffold.[5,6] Here, the oxazoline **1** is first ring-opened with the azide ion as nucleophile, and the ensuing azide **2** is subsequently reduced to the monoacylated 1,2-diamine **3** (Scheme 1). The azide source is usually $TMSN_3$ in a high-boiling alcohol, such as *t*BuOH.[6,7] For example, the corresponding oxazoline-ring-opening reaction with $TMSN_3$ in *t*BuOH to introduce the *N*-(2-aminoethyl)acylamide moiety in the neuraminidase inhibitor Zanamivir (Scheme 1) was performed at 80 °C for 10.5 h on up to 600 g scale.[6c] It should be noted that $TMSN_3$ rapidly releases volatile hydrazoic acid (HN_3, b.p. 37 °C) in the presence of protic solvents, such as alcohols.[8b] HN_3 is an extremely explosive and toxic material



Scheme 1. Two-step synthesis of selectively monoacylated 1,2-diamines starting from 2-oxazolines.

and, hence, these batch protocols are hardly suitable for reactions on scale. Therefore, alternative strategies that avoid the use of $TMSN_3$ to introduce the *N*-(2-aminoethyl)acylamide moiety have been developed.[8]

Recently, we have described a general and scalable method for the synthesis of 5-substituted-1*H*-tetrazoles through cycloaddition of organic nitriles with HN_3 by using continuous-flow technology.[9] Key to this protocol is the in situ generation of HN_3 from an aqueous solution of NaN_3 and AcOH inside a microreactor environment by using a two-feed concept. Driven by the ever increasing demand for cost-effective and safe chemical processes, the interest in continuous-flow and microreactor technology in the fine chemical industry increased tremendously in recent years.[10,11] A continuous-flow approach generally allows more drastic reaction conditions (e.g., high temperatures/pressures) to be used, even when hazardous reagents or intermediates are involved.[12] Heat and mass transfer is very fast at the scales used in flow systems (channel or capillary diameters of ≈50–1000 μm), and the volumes processed at any time are kept very small.[10–13] Synthetic intermediates can be generated and consumed in situ in a closed system by combining multiple reagent streams, which eliminates the need to handle or store toxic, reactive, or explosive intermediates.[14] A further important advantage of microreaction technology is the ease with which reaction conditions can be scaled to production scale capacities, for example, through the operation of multiple systems in parallel or related strategies.[13]

As an extension of our earlier HN_3 microreactor work,[9] we herein report the ring-opening of various 2-oxazolines **1** to the corresponding β-azido carboxamides **2** with in situ

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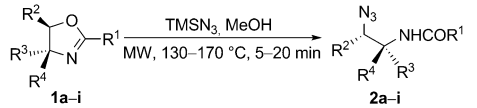
generated HN_3 under continuous-flow conditions.[14] In contrast to our previous strategy, HN_3 is now generated inside the microreactor environment by solvolysis of $TMSN_3$ with MeOH and consumed inside the heated-coil reactor by a S_N2 ring-opening reaction with the oxazoline heterocycles. $TMSN_3$ was the reagent of choice for this reaction, in particular because it is highly soluble in a variety of organic solvents. The effluent product mixture can be directly subjected to hydrogenation in a continuous-flow-hydrogenation device without the need to isolate and purify the intermediate azides **2**. Any excess of HN_3 is destroyed inside the flow hydrogenation reactor, and monoacylated 1,2-diamines of type **3** are isolated as the final products (Scheme 1).

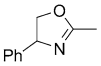
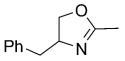
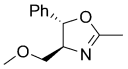
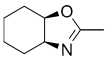
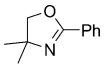
Initial optimization experiments were performed by using the commercially available and structurally very simple 2-methyl-2-oxazoline (**1a**) as model substrate. Following the "microwave-to-flow" paradigm,[15] our optimization studies were first executed on a small scale (<1 mL reaction volume) in a microwave batch reactor. Best results were obtained by using MeOH as the solvent. The ring-opening was considerably slower in *i*PrOH or *t*BuOH as the solvent, and did not proceed at all in aprotic solvents, such as THF or MeCN (for further details see Table S1 in the Supporting Information). Our observations are in good agreement with those made by Saito et al. and indicate that the reactive species in this process is indeed HN_3, which is generated in situ from $TMSN_3$ and the protic solvent.[7c] By utilizing MeOH as the solvent and employing 1.2 equivalents of $TMSN_3$, the ring-opening reaction was accomplished within 5 min at 130 °C (8 bar pressure) in the microwave batch reactor (Table 1). The reaction was remarkably clean, and the product was isolated in high purities (>99% by GC-FID and ^{1}H NMR spectroscopy) and almost quantitative yield after simple evaporation of the solvent and any excess of reagent under vacuum. Similar results were obtained by using 2-ethyl-2-oxazoline (**1b**) as the starting material. The 2-phenyl derivative **1c** and the 4-substituted 2-methyl oxazolines, **1d** and **1e**, however, required somewhat harsher reaction conditions and for the 4,5-substituted oxazolines, **1f** and **1g**, the amount of $TMSN_3$ was increased to 1.3 equivalents (Table 1). As expected, the ring-opening for oxazolines **1f** and **1g** occurred stereospecifically by inversion on carbon C5 (for details and spectra, see the Supporting Information).[6,7]

Under these general reaction conditions, only the 4,4-dimethyl substituted oxazolines **1h** and **1i** did not undergo ring-opening in an acceptable reaction time. Full conversion of these difficult substrates to the corresponding azides was not obtained even at temperatures of 160 °C (18 bar). After heating for 20 min at 160 °C, the conversion was 74% for 2,4,4-trimethyl oxazoline **1h** with 1.2 equivalents of $TMSN_3$, and reaction with 4,4-dimethyl-2-phenyl derivative **1i** gave only 15% conversion after 25 min at 160 °C with 1.3 equivalents of $TMSN_3$. Although the reactions remained fairly clean even at these high temperatures, we screened a number of different catalysts to accelerate the oxazoline ring-opening reaction with these two substrates (for a detailed description of these investigations, see the Supporting Information). The S_N2 ring-opening of oxazolines is generally catalyzed by electrophiles.[1,2] In particular, hard, oxophilic Lewis acids, such as $Yb(OTf)_3$, and electrophiles, such as *N*-iodosuccinimide (NIS) and *N*-bromosuccinimide (NBS), increased the reaction rate significantly. Unfortunately, the purity of the reaction was somewhat compromised in the presence of acidic catalysts. Ultimately, we discovered that the reaction is considerably accelerated by catalytic amounts (10 mol%) of triethylamine (TEA) without decreasing the selectivity for the ring-opening reaction. Presumably, TEA assists in the release of HN_3 from $TMSN_3$ (see the Supporting Information). The azides **2a** and **2b** could be isolated by simple evaporation of the solvent, whereas azides **2c**–**2i** were further purified by extraction with 0.5 N HCl/$CHCl_3$ to give products with high purity (>99% by GC-FID and ^{1}H NMR spectroscopy, Table 1).

In the above batch-type experiments, HN_3 could be detected in the headspace above the solvent mixture immediately upon mixing $TMSN_3$ with MeOH (Figure S1 in the Supporting Information).[16] Given the numerous safety issues in handling HN_3,[8] we therefore envisaged a continuous-flow strategy for the ring-opening of oxazolines, whereby HN_3 is generated in situ in a microreactor environment

Table 1. Synthesis of *N*-(2-azidoethyl)acylamides **2a**–**2i** under microwave batch conditions.[a]

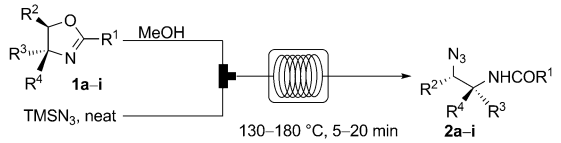


	Substrate	*t* [min]	*T* [°C]	$TMSN_3$ [equiv]	Yield [%][b]
1a		5	130	1.2	97
1b		5	130	1.2	99
1c		10	140	1.2	96
1d		10	130	1.2	90
1e		10	130	1.2	96
1f		10	140	1.3	95
1g		10	140	1.3	88
1h		15	160	1.3	87[c]
1i		20	170	1.3	69[c]

[a] Conditions: oxazoline **1** (1.8 mmol), $TMSN_3$ (1.2–1.3 equiv), MeOH (300 μL), single-mode microwave reactor (Biotage Initiator). [b] Products **2a** and **2b** were isolated by removing the solvent and excess of reagent under reduced pressure; products **2c**–**2i** were further purified by extraction with 0.5 N HCl/$CHCl_3$. [c] TEA (10 mol%) was used as the catalyst.

and subsequently consumed by the reaction with the oxazoline. This concept necessitates that the oxazoline starting materials, dissolved in MeOH, and the $TMSN_3$ reagent are in two separate feeds. The hazardous and toxic HN_3 is then generated inside a suitable mixer upon combination of the two streams. In a subsequent high-temperature coil reactor the ring-opening reaction occurs, before the reaction mixture is thermally quenched by a heat exchanger and exits the continuous-flow system through a back-pressure regulator (Table 2).

Table 2. Continuous-flow synthesis of *N*-(2-azidoethyl)acylamides.[a]



Substrate	Flow rate A/B [mL min^{-1}]	*c* feed A [M]	*t* [min]	*T* [°C]	$TMSN_3$ [equiv]	Yield [%][b]
1a	2.45/1.55	4.0	5	130	1.2	93
1b	2.45/1.55	4.0	5	130	1.2	95
1c	1.25/0.75	3.8	10	140	1.2	94
1d	1.35/0.65	3.05	10	140	1.2	74
1e	1.35/0.65	3.05	10	140	1.2	91
1f	1.40/0.60	2.5	10	150	1.3	91
1g	1.25/0.75	3.5	10	150	1.3	67
1h	0.80/0.50	3.65	15.4	170	1.3	77[c]
1i	0.70/0.30	2.5	20	180	1.3	59[c]

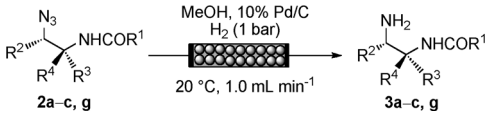
[a] Conditions (Uniqsis FlowSyn reactor): feed A: oxazoline solutions (2 mL); feed B: neat $TMSN_3$; the applied equivalents of $TMSN_3$ follow from the concentration of the oxazoline in feed A and the relative flow rates of the two feeds; reaction times refer to residence times in the heated-coil reactor (20 mL stainless steel, 34 or 52 bar back-pressure regulator, see the Supporting Information for details). [b] For isolation conditions see Table 1, footnote [b]; purities of the isolated azide products were identical to those obtained under microwave-batch conditions. [c] TEA (10 mol%) was used as the catalyst.

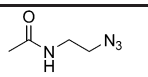
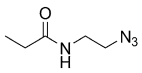
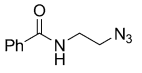
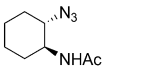
The very high solubilities of the tested oxazolines **1a–i** in MeOH allowed the use of extremely concentrated mixtures of the oxazoline starting materials (2.5–4 M, feed A). The $TMSN_3$ was fed into the reactor as the neat reagent through a second pump (feed B). For an initial proof-of-concept study, we introduced 2 mL of the oxazoline solutions into the flow reactor (Uniqsis FlowSyn) equipped with a 20 mL stainless-steel coil (1.0 mm internal diameter, ca. 25 m length). Flow rates of the two streams, A and B, were selected to reproduce the microwave batch experiments. After completion of the process, the whole reaction mixture was collected (plus pre- (5 mL) and post-collection (10 mL)), analyzed (GC-FID), and the azide products **2a–2i** were isolated (Table 2). The reaction temperatures were adjusted slightly for some of the ring-opening reactions to account for dispersion/diffusion of the introduced reaction "plug". The somewhat reduced conversions and isolated product yields, compared with the microwave batch experiments, are mainly caused by axial dispersion of the reaction plug and the consequent dilution of the reaction mixture.[17] These issues do not arise, when the reactor is operated continuously (see below) or can be circumvented by "steady-state collection" (see the Supporting Information).

By employing oxazoline **1h** as the model substrate, the flow reaction was repeated on a tenfold scale without changing or reoptimizing the other reaction parameters. Hence, a solution of oxazoline (3.65 M) in MeOH (20 mL) (oxazoline **1h** (73 mmol) and TEA (7.3 mmol), feed A) and neat $TMSN_3$ (feed B) were pumped into the mixer at flow rates of 0.80 and 0.50 mL min^{-1}, respectively. During this period, $TMSN_3$ (12.5 mL, 1.3 equiv) was consumed in the process. The reaction mixture passed through the coil reactor heated at 170 °C and left the reactor via the heat exchanger and a 52 bar back-pressure regulator. Again, the whole reaction mixture was collected (plus pre (5 mL) and post collection (10 mL)) and the desired azide **2h** was isolated in high purity and yield (9.6 g, 84%), comparable to the results achieved under microwave batch conditions on a 1.8 mmol scale (Table 1).[18] This corresponds to a productivity of approximately 0.5 kg of *N*-(2-azidoethyl)acylamide **2h** per day.

Following our two-step continuous-flow ring-opening/hydrogenation strategy to access the desired *N*-(2-aminoethyl)acylamides **3** (Scheme 1), the synthesized *N*-(2-azidoethyl)acylamides **2a–i** (Table 2) were reduced with H_2 over Pd/C in MeOH as the solvent in continuous-flow mode to the monoacylated diamines **3a–i** (Table 3). Monoacylated 1,2-diamines are a particularly valuable class of substrates, as highlighted in Scheme 1, but are often difficult to synthesize selectively.[19] For hydrogenation reactions employing heterogeneous catalysts, microreactor and continuous-flow technology are particularly attractive.[20] Here, the hydrogen/substrate mixture is pumped through packed catalyst columns by high-pressure pumps. Due to the large interfacial areas and the short diffusion paths in the packed columns, very ef-

Table 3. Continuous-flow reduction of *N*-(2-azidoethyl)acylamides.[a]

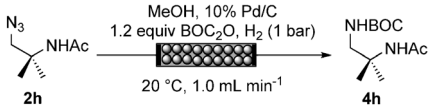


	Substrate	Yield [%][b]
2a		96
2b		99
2c		95
2g		95

[a] Conditions (H-Cube, ThalesNano): *N*-(2-azidoethyl)acylamides **2** (0.1 M solutions, 2 mmol scale) were reduced in a continuous-flow hydrogenation reactor. [b] The products were isolated by removing MeOH under reduced pressure.

ficient gas–liquid–solid interactions, and thus hydrogenation, takes place.[20] Reduction of the azides **2a–c** and **2g** following a standard room-temperature-hydrogenation method[21] in a continuous-flow hydrogenator (H-Cube) gave the pure monoacylated diamines **3a–c** and **3g** after evaporation of the solvent (Table 3).

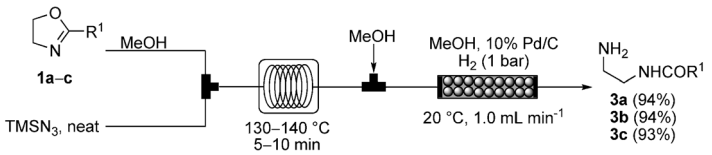
Interestingly, the dimethyl-substituted azide **2h** provided a mixture of the two isomeric acylated diamines **3h** and **3h′**. Apparently, the *N*-acetyl group migrates upon reduction and/or during workup.[22] Small amounts of the rearranged monoacyl-1,2-diamines were also detectable after reduction of the other 4- or 4,5-substituted *N*-(2-azidoethyl)acylamides **2d** and **2e**, and even the benzoyl group in **3i** underwent migration under the chosen reaction conditions (see the Supporting Information for details). Gratifyingly, the migration of the acetyl group can be easily prevented by interception of the freshly formed amino group by di-*tert*butyl dicarbonate (BOC_2O) as demonstrated for the reduction of azide **2h** (Scheme 2). Hence, azide **2h** and BOC_2O (1.2 equiv) were



Scheme 2. Preparation of the BOC-protected *N*-(2-aminoethyl)acetylamide **4h**.

dissolved in MeOH and the mixture was pumped through the continuous-flow hydrogenator (H-Cube). The crude BOC-protected *N*-(2-aminoethyl)acetylamide **4h** was isolated in excellent purities (98% by GC-FID), without any sign of rearrangement, in 94% yield after evaporation of the solvent and washing the crude product with petroleum ether.

From a processing standpoint, it is important to note that the crude *N*-(2-azidoethyl)acylamide reaction streams, obtained through continuous-flow ring-opening of 2-oxazolines with HN_3 (Table 2), can be used directly for the flow hydrogenation step without prior isolation/purification of the azide intermediates. For this purpose, the highly concentrated crude azide mixtures leaving the coil reactor (FlowSyn) were diluted with MeOH and directly introduced into the flow hydrogenator (H-Cube) (Scheme 3). Apparently,



Scheme 3. Two-step continuous-flow synthesis of *N*-(2-aminoethyl)acylamides **3a–c**.

$TMSN_3$ does not interfere with the hydrogenation reaction, and importantly, from a safety standpoint, no HN_3 was detectable in the reaction mixtures after the reduction.[16] Therefore, this hydrogenation step additionally serves as an efficient method to destroy excess/unreacted HN_3 formed in the ring-opening process. As exemplified for oxazoline substrates **1a–c**, this combined two-step continuous-flow strategy provided the acylated amines **3a–c** in excellent purities and product yields (Scheme 3).

In conclusion, we have demonstrated that variously substituted 2-oxazolines **1** can be efficiently and safely ring-opened to provide *N*-(2-azidoethyl)acylamides **2** by using a high-temperature/pressure continuous-flow approach. Key to the success of this protocol is the in situ generation of toxic and explosive HN_3 within the microreactor environment from $TMSN_3$ and MeOH. The resulting *N*-(2-azidoethyl)acylamides **2** can be further reduced directly to *N*-(2-aminoethyl)acylamides **3** by using a continuous-flow hydrogenation protocol. The selectively protected 1,2-diamine scaffold prepared by this method constitutes an important structural moiety in several pharmaceutical products.

Experimental Section

General synthesis of *N*-(2-aminoethyl)acylamides 3 (Scheme 3): Appropriate amounts of oxazolines **1a–c** (Table 2) were weighed into a volumetric flask (2 mL), and the flask was filled to the mark with MeOH (feed A). $TMSN_3$ was added to a second flask (feed B). Streams A and B were mixed together at the indicated flow rates in a T-mixer at RT, and the resulting stream was passed through the stainless-steel reactor coil (20 mL heated volume) heated at the indicated temperatures (Table 2). After passing the coil reactor, the mixtures were cooled in the plate-heat exchanger to RT and left the reactor through a 34 bar back-pressure regulator. The entire reaction mixtures were collected (plus pre (5 mL) and post collection (10 mL)) in a graduated cylinder, and the product mixtures were diluted with MeOH to give a 0.1 M solution. 20 mL of these solutions were then pumped through the H-Cube (10% Pd/C, 20 °C, 1 mL min^{-1} flow rate, full H_2 mode). The effluent reaction mixtures were collected, and the solvent removed under vacuum. This procedure afforded the pure *N*-(2-aminoethyl)acylamides **3a** and **3b** (>99% by GC-FID) in 94% yield. The crude *N*-(2-aminoethyl)benzamide **3c** was isolated in 93% yield after washing with anhydrous Et_2O (2×2 mL) to remove unreacted 2-phenyl-2-oxazoline **1c**.

Acknowledgements

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Keywords: hydrazoic acid · hydrogenation · microreactors · oxygen heterocycles · synthetic methods

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