

# Safe Generation and Synthetic Utilization of Hydrazoic Acid in a Continuous Flow Reactor

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Hydrazoic acid (HN<sub>3</sub>) was used in a safe and reliable way for the synthesis of 5-substituted-1*H*-tetrazoles and for the preparation of *N*-(2-azidoethyl)acylamides in a continuous flow format. Hydrazoic acid was generated in situ either from an aqueous feed of sodium azide upon mixing with acetic acid, or from neat trimethylsilyl azide upon mixing with methanol. For both processes, subsequent reaction of the in situ generated hydrazoic acid with either organic nitriles (tetrazole formation) or 2-oxazolines (ring opening to β-azido-carboxamides) was performed in a coil reactor in an elevated temperature/pressure regime. Despite the explosive properties of HN<sub>3</sub>, the reactions could be performed safely at very high temperatures to yield the desired products in short reaction times and in excellent product yields. The scalability of both protocols was demonstrated for selected examples. Employing a commercially available benchtop flow reactor, productivities of 18.9 g/h of 5-phenyltetrazole and 23.0 g/h of *N*-(1-azido-2-methylpropan-2-yl)acetamide were achieved.

**Keywords:** flow chemistry, hydrazoic acid, microreactor, process intensification, tetrazoles

## 1. Introduction

Hydrazoic acid (HN<sub>3</sub>), a gas of “highly peculiar, dreadfully pungent smell,” was discovered by Theodor Curtius in the 1890s by acidification of sodium azide [1]. HN<sub>3</sub> is a very volatile (bp. 37 °C), dangerously explosive, and toxic compound [2]. The acute toxicity of hydrazoic acid through inhalation and other routes of exposure is comparable to that of hydrogen cyanide, and its vapor causes violent headaches, dizziness, decreased blood pressure, convulsion, and death [2].

The explosion risk of organic azides decreases with diminishing fraction of N<sub>3</sub> in the molecular mass. HN<sub>3</sub> itself is, hence, dangerously sensitive to heat, friction, or impact. Solutions with a HN<sub>3</sub> content in excess of 20% can decompose explosively, and explosive gas-phase mixtures of HN<sub>3</sub> in N<sub>2</sub> have been reported at concentrations as low as 8% [2]. The detonation speed of HN<sub>3</sub> is around 8000 m/s and the decomposition enthalpy is greater than that of trinitrotoluene (TNT) [2]. Explosion of a few tenths of a milliliter of liquid HN<sub>3</sub> can destroy a complete laboratory-scale production unit. The explosion of grams, kilograms, or even tons of HN<sub>3</sub> would be a disaster for employees and plant equipment alike [3]. The fact that azide chemistry, outside of the production of explosives, has only reached a commercial production volume of 1000 t/a during the last 30–40 years is largely due to the hazards associated with azides [3]. In particular, HN<sub>3</sub> itself has little significance as reagent in organic synthesis, and the greatest care must be exercised whenever HN<sub>3</sub> is expected to be formed during a reaction.

Continuous flow and microreactor technology provides a means to address safety issues and process challenges associated with reactions involving explosive or otherwise hazardous materials [4, 5]. Not surprisingly, therefore, several continuous flow processes involving toxic, explosive, or corrosive reagents and gases have been described in the past few years [6, 7]. In a continuous flow approach, the volumes processed at any time are kept very small and the total hazard present is thus kept to

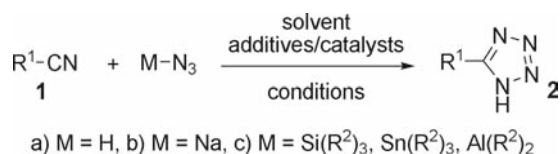
a minimum [6–8]. The characteristics of microreaction technology (i.e., fast heat and mass transfer, and high pressure resistance of capillaries with small inner diameters) often allow temperatures to be used which would be unsafe in traditional batch reactors [9]. The shorter reaction times at higher temperatures, in turn, allow smaller reactor volumes at a given throughput and, hence, a more economical and safer overall process [9]. Synthetic intermediates can be generated, consumed, and finally quenched inside a closed, pressurized system by combining multiple reagent streams, without the need to handle or store toxic, reactive, or explosive intermediates [4–7]. A further important advantage of continuous flow/microreaction technology is the ease with which reaction conditions can be scaled to production-scale capacities, for example, by increasing the running time or by operation of multiple systems in parallel [8].

Despite the risks associated with azides, interest in azide chemistry has steadily grown and an astonishing versatility of preparative and synthetic applications was uncovered in recent years [3, 10]. Industrial interest in azide chemistry began with their use in the synthesis of heterocycles, such as triazoles and tetrazoles, and as a functional group in pharmaceuticals, such as azidonucleosides [10]. Several safety issues have to be addressed for azide reactions on a manufacturing scale. The specific rationale for the development of many processes was to arrive at conditions that would avoid the direct use or liberation of HN<sub>3</sub>. In protic solvents, however, equilibrium concentrations of HN<sub>3</sub> are unavoidable. Furthermore, on the bases of reactivity, atom economy, waste generation, and economical considerations, HN<sub>3</sub> would be the ideal reagent for many applications involving azide functionalities.

We have recently developed two safe and scalable transformations involving HN<sub>3</sub> as reagent and reported our results in two communications [11, 12]. In these instances, HN<sub>3</sub> was generated from easy to handle and relatively safe precursors inside a continuous flow reactor and consumed in a subsequent residence coil. The full details of both processes with an extended discussion contrasting both protocols are herewith described in this full paper.

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**Scheme 1.** General azide–nitrile addition strategy for the synthesis of tetrazole derivatives



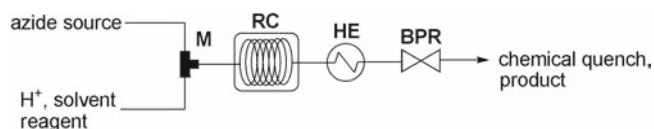
## 2. Results and Discussion

**2.1. General Outline of Continuous Flow Strategy.** The first example involves the synthesis of 5-substituted-1*H*-tetrazoles **2** by a Huisgen 1,3-dipolar cycloaddition of HN<sub>3</sub> to nitriles of type **1** (Scheme 1) [11]. For economical reasons and atom economy, sodium azide (NaN<sub>3</sub>) was selected as an inexpensive azide source. NaN<sub>3</sub> is rather soluble in water, but virtually insoluble in organic solvents. However, in continuous flow/microreactor processing, fully homogeneous reaction media are highly desirable. Therefore, we envisaged to combine an aqueous solution of sodium azide with an acidic stream containing the respective nitrile. Aqueous solutions of ca. 10% HN<sub>3</sub> are safe to handle, while solutions with a hydrazoic acid content in excess of 20% are liable to decompose explosively [2]. The pH of a saturated NaN<sub>3</sub> solution is around 9.5 and the concentration of HN<sub>3</sub> (p*K*<sub>a</sub> 4.6) in the solution is therefore just in the order of 5 × 10<sup>-5</sup> M and, thus, far below the safety limit. The aqueous NaN<sub>3</sub> is pumped into the reactor and combined with a stream containing both the Brønsted acid and the nitrile starting materials. The combined stream is then passed through a heated RC where the [3+2] cycloaddition of the azide to the nitrile takes place (Figure 1).

The second example is a ring opening reaction of 2-oxazolines **3** with HN<sub>3</sub> to prepare the *N*-(2-azidoethyl)acylamide scaffold **4** (Figure 7) [12]. 2-Oxazolines are rather prone to hydrolysis and the intended nucleophilic ring opening is thus incompatible with an aqueous reaction media. Trimethylsilyl azide (TMSN<sub>3</sub>) was chosen as an organic HN<sub>3</sub> precursor for this reaction. TMSN<sub>3</sub> is a liquid (bp 95 °C) that is soluble in various organic solvents and is without immediate explosive properties. However, it is well known that neat TMSN<sub>3</sub> or TMSN<sub>3</sub> dissolved in aprotic solvents hardly reacts as nucleophile in this reaction. Hence, a TMSN<sub>3</sub> stream is combined with an alcoholic solvent stream (MeOH) to release HN<sub>3</sub>. The in situ formed HN<sub>3</sub> then reacts with 2-oxazolines in the RC to the desired products.

After the cycloaddition/ring opening reaction in the RC, the post-reaction stream can be thermally quenched in a heat exchanger (HE) and the cooled mixture then exits the continuous flow system through a back-pressure regulator (BPR). The whole system is run liquid-filled without vapor-phase headspace, and the risk associated with volatile HN<sub>3</sub> is hence significantly reduced. The excess of HN<sub>3</sub> in the effluent product stream finally can be conveniently destroyed by a chemical quench step, for example, by the reaction with aqueous NaNO<sub>2</sub> or ceric ammonium nitrate [13]. Alternatively, HN<sub>3</sub> can be scavenged in-line from the post-reaction stream [14].

The instrument used for both continuous flow transformations was the Uniqsis FlowSyn reactor (Figure 2) [15]. The



**Figure 1.** Flow concept for handling of HN<sub>3</sub> as reagent

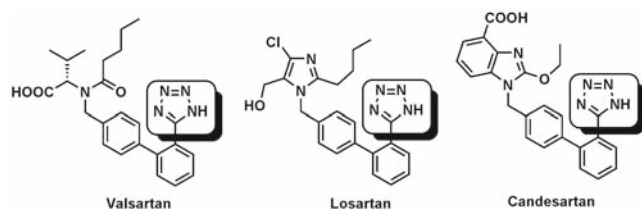


**Figure 2.** FlowSyn reactor from Uniqsis Ltd [15]

reactor is furnished with two HPLC pumps, with each pump allowing flow rates from 0.02 to 10 mL/min, giving a maximum total flow rate of 20 mL/min. The flow system can be equipped with coil reactors of variable lengths and materials. The coil reactor is heated on an aluminum heating block (maximum temperature 260 °C) and can be connected to a plate HE. The product mixture leaves the reactor through a BPR (maximum pressure 69 bar).

For both syntheses, initial optimization studies were executed in a microwave batch reactor employing sealed, pressure-resistant glass vessels. The use of microwave batch technology allows a quick screening of reaction conditions (solvents, reagents, stoichiometry, etc.) in a temperature/pressure regime approaching that accessible in commercially available continuous flow reactors. Dedicated microwave reactors are hence ideal tools for initial reaction optimization in high-T/p process windows (“microwave-to-flow” paradigm) [16]. Optimization runs were performed on a millimolar scale (~1–2 mmol substrate, ≤1.5 mL solvent) in a temperature range up to 220 °C, generating internal pressures up to 20 bar depending on the solvent used.

**2.2. 1,3-Cycloaddition of HN<sub>3</sub> on Organic Nitriles.** Interest in tetrazole chemistry has been increasing rapidly over the past few years, mainly because of the role of the tetrazole moiety in medicinal chemistry as a metabolically stable surrogate for carboxylic acid functionalities [17]. Tetrazoles often offer improved oral bioavailability and pharmacokinetic profiles compared to their carboxylic acid counterparts [17]. The majority of tetrazole-based drug substances are aryl tetrazoles. In fact, a great part of these structures, many of which are structural derivatives of the nonpeptidic selective angiotensin II receptor antagonist Losartan, contain the biphenyl tetrazole motif (Figure 3). Additional important applications for tetrazoles are found in coordination chemistry, organic catalysis, and the materials sciences. Furthermore, tetrazoles are versatile intermediates in the synthesis of nitrogen-containing heterocycles via a Huisgen rearrangement [18].



**Figure 3.** Angiotensin II receptor antagonists (Sartans)

Although the first published methods for the preparation of 5-substituted tetrazoles indeed involved the addition of  $\text{HN}_3$  gas to organic nitriles in unpolar solvents such as toluene [19], these protocols are hardly used today and were quickly replaced by more practical procedures. Nowadays, the most common synthetic approach to prepare 5-substituted-1*H*-tetrazoles involves heating of certain inorganic azide salts with a nitrile solution, typically at temperatures  $>100$  °C (Scheme 1). A wide variety of inorganic azide salts are competent azide donors, but in the majority of cases sodium azide has been used as the azide source. Unfortunately, the energy barrier for the direct addition of the azide ion to a nitrile is fairly high and this transformation is generally too slow to be synthetically useful [20]. However, when a proton is available, the reaction seems to proceed via an imidoyl azide intermediate [20], and similar to related reactions involving nucleophilic attack on nitriles, such as acidic hydrolysis of a nitrile to an amide or the Pinner synthesis of imidates, the azide–nitrile addition reaction is greatly accelerated by acid catalysis. A broad variety of acidic catalysts, ranging from soluble proton [21] or Lewis acids [22] to various heterogeneous [23] and nanocrystalline catalysts [24], have been reported as suitable promoters for the desired azide–nitrile addition process. Mild acids are usually sufficient. Indeed, in most cases, sodium azide is used in combination with an ammonium halide as additive in dipolar aprotic solvents such as *N,N*-dimethylformamide (DMF) or *N*-methylpyrrolidone (NMP) [25]. Further, azide–nitrile cycloaddition reactions in the presence of stoichiometric or substoichiometric amounts of zinc bromide or chloride as additives in water as solvent have become increasingly popular in the last few years [22]. In addition, trimethylsilyl [26], trialkyl tin [27], and organoaluminum azides [28] have been introduced as comparatively safe alternatives to inorganic azide salts, which have the additional benefit of being soluble in organic solvents (Scheme 1).

An evaluation of existing protocols for batch tetrazole syntheses made the challenges of converting batch to flow conditions immediately apparent. Apart from the fact that most of the available procedures require reaction times of many hours or even days to obtain high conversions, in many instances the reaction mixtures are heterogeneous, due to the presence of reagents, additives, or catalysts of low solubility in the chosen solvent [19–28]. However, reaction times (= residence times) in flow should ideally be in the order of a few minutes to allow a high throughput. With this background, an optimization campaign was started selecting 2,2-diphenylacetonitrile **1a** as a model compound for tetrazole formation. Optimization runs were performed on a 1-mmol scale at temperatures up to 220 °C. Initial experiments were performed in a single-mode microwave reactor but, to increase screening throughput, we subsequently moved to a parallel format utilizing a standard hotplate/magnetic stirrer in combination with a silicon carbide (SiC) reaction block with a  $6 \times 4$  deep well matrix in which pressure-resistant 5 mL Pyrex screw cap reaction vials were placed [29]. Owing to the high thermal conductivity and effusivity of SiC, heating of the block is very uniform and heat transfer to the reaction mixture inside the Pyrex vial is very rapid, simulating a microwave dielectric heating experiment [29, 30]. Indeed, optimiza-

tion results obtained under microwave conditions were identical to those found in the conventionally heated SiC reaction block at the same temperature, with the additional benefit that in the hotplate experiments the homogeneity of the reaction mixtures could be easily evaluated by visual inspection.

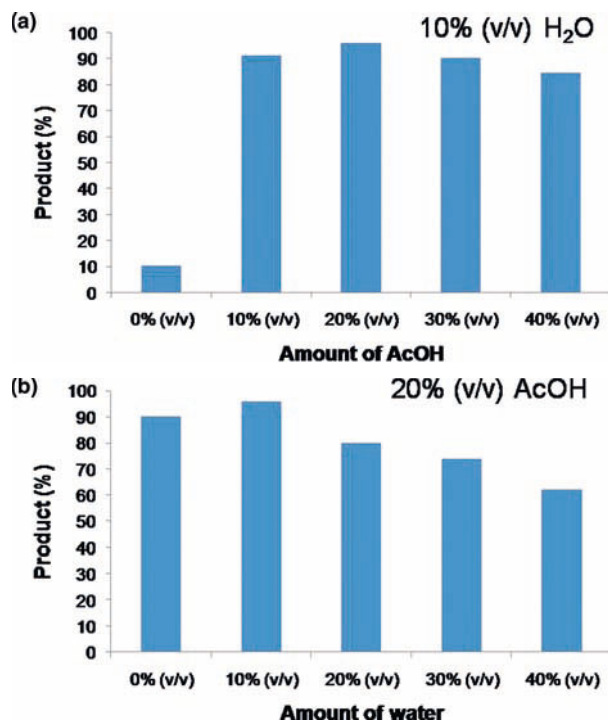
The starting point for our optimization study was the classical protocol developed by Finnegan and Lofquist in 1958, employing  $\text{NaN}_3$  as azide source in combination with  $\text{NH}_4\text{Cl}$  as additive in DMF as solvent [25a]. Full conversion of nitrile **1a** was obtained with 2 equiv of  $\text{NaN}_3$  and 1 equiv of  $\text{NH}_4\text{Cl}$  after 3 h at 160 °C in the microwave batch reactor. Unfortunately, an unidentified impurity was detectable in all reactions using  $\text{NH}_4\text{Cl}$  as additive (up to 35%). This side product was not observed when triethylammonium chloride (TEACl) was used as the additive and, furthermore, the reaction was somewhat faster with the latter additive. Conversions  $>90\%$  were obtained after heating for 2 h at 160 °C with 2 equiv of  $\text{NaN}_3$  and 1 equiv of TEACl using DMF or NMP as solvent. The reaction was remarkably clean and virtually no side products were detectable by HPLC-UV monitoring. Increasing the amounts of  $\text{NaN}_3$  to 3 equiv reduced the required reaction time to just 1 h at 160 °C. However, since both  $\text{NaN}_3$  and TEACl (or  $\text{NH}_4\text{Cl}$ ) are insoluble in DMF or NMP, and the addition of water as cosolvent decreased the reaction rate and purity of the reaction, we screened a range of additional catalysts, and a variety of solvents and solvent/water mixtures. Zn salts, such as  $\text{ZnBr}_2$ , are rather soluble in various organic solvents and catalyze the azide–nitrile cycloaddition considerably [22a]. However, quite large amounts of the zinc salt are required for an efficient reaction (commonly stoichiometric amounts are used) and significant amounts of the amide were formed in organic solvent/water systems. Better results were obtained employing Brønsted acids in NMP. There was no apparent correlation between acid strength and the acceleration of the reaction. Poor results were obtained with aqueous HCl and glycolic acid (glycolic acid is not soluble in NMP). Best results were obtained with acetic acid and formic acid (Table 1).

Naturally,  $\text{NaN}_3$  forms  $\text{HN}_3$  immediately upon contact with the Brønsted acid. For the continuous flow protocol, we thus envisaged to mix  $\text{NaN}_3$  with the acidic stream just inside the flow reactor. This requires  $\text{NaN}_3$  dissolved in a suitable solvent.  $\text{H}_2\text{O}$  is clearly the best solvent for this purpose and, therefore, we next examined the influence of  $\text{H}_2\text{O}$  on the reaction. The NMP/AcOH/ $\text{H}_2\text{O}$  solvent composition was therefore varied for the reaction of nitrile **1a** with 3 equiv of  $\text{NaN}_3$  while the total volume of the solvent mixture was kept constant. For a given proportion of  $\text{H}_2\text{O}$ , the fastest reactions were generally achieved with 20 vol % of AcOH. When no AcOH was used, the reaction rate decreased sharply (Figure 4a). For low amounts of

**Table 1.** Influence of different Brønsted acids on the conversion **1a** → **2a** in NMP (HPLC-UV at 215 nm)<sup>a</sup>

Product (%)	Product (%)		
85% $\text{H}_3\text{PO}_4$	36	$\text{CH}_3\text{SO}_3\text{H}$	34
conc. HCl	27	$\text{F}_3\text{COOH}$	36
AcOH	53	95% Formic acid	47
$\text{H}_3\text{BO}_3$	37	Glycolic acid	28

<sup>a</sup>Conditions: 1 mmol **1a**, 1.1 equiv acid and 2 equiv  $\text{NaN}_3$  in 1 mL of NMP. Pyrex screw cap reaction vials were heated for 35 min in a  $6 \times 4$  SiC heating block preheated to 160 °C.

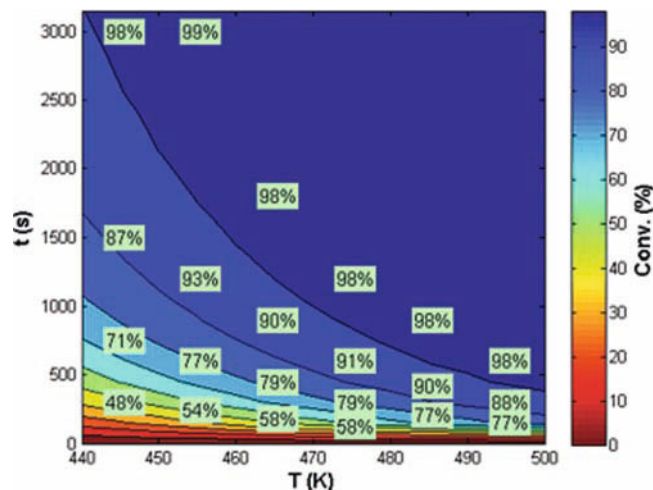


**Figure 4.** Effect of NMP/AcOH/H<sub>2</sub>O solvent composition (HPLC at 215 nm). (a) Increasing amounts of AcOH at a constant proportion of H<sub>2</sub>O (10%); (b) Increasing amounts of H<sub>2</sub>O at a constant proportion of AcOH (20%). Conditions: 1 mmol **1a**, 3 equiv NaN<sub>3</sub> in 1.5 mL of NMP/AcOH/H<sub>2</sub>O. Pyrex screw cap reaction vials were heated for 30 min in a 6 × 4 SiC heating block preheated to 180 °C

AcOH (≤20 vol %), there was also an optimum for the water content. The reaction rate decreased with increasing amounts of water, but when water was not used as a cosolvent, the obtained conversions dropped again, possibly because the solubility of NaN<sub>3</sub> decreased (Figure 4b). The required amount of water for the optimum reaction decreased with increasing proportion of AcOH and when the amount of AcOH was increased above ~30%, water was generally detrimental.

Our final optimal batch reaction conditions comprised a solution of 1 mmol of the nitrile **1a** and 2 equiv of NaN<sub>3</sub> in 1 mL of NMP/AcOH/H<sub>2</sub>O in a ratio of 7:2:1. The reaction could be performed at astonishingly high temperatures with remarkable purity (Figure 5). At 220 °C, nitrile **1a** was virtually fully converted to the desired tetrazole within 10 min in the microwave batch reactor. The small amounts of impurities formed during the reaction, and remaining starting materials (<4%; HPLC at 215 nm) were simply removed by pouring the crude reaction mixture into a saturated aqueous NaHCO<sub>3</sub> solution and extraction with an organic solvent (e.g., toluene). NaNO<sub>2</sub> was added to the aqueous solution to destroy any excess of NaN<sub>3</sub> and the pure tetrazole compound precipitated from the solution after acidification with conc. HCl (85% isolated yield) [13].

As expected, evaluating the scope and limitation of the cycloaddition process, aromatic nitriles **1d–1n** reacted considerably faster compared to the sterically hindered diphenylacetone nitrile **1a** (Table 2, MW). Complete conversions of these substrates were obtained after 5–6 min reaction time at 220 °C under the optimized microwave conditions. The tetrazoles were isolated in pure form and in high yields by transferring the reaction mixture into a solution of 0.1 M NaNO<sub>2</sub> in H<sub>2</sub>O (ca 10 mL), followed by precipitation by adjusting the pH to around 1 (caution: gas evolution!) [13]. The comparatively lower isolated product yields for tetrazoles **2m** and **2n** are due to the rather high water solubilities of these amphoteric tetrazoles. The



**Figure 5.** Conversion of nitrile **1a** to tetrazole **2a** as a function of reaction time and reaction temperature. Conversions indicated in the boxes are experimental results (HPLC peak area integration; conditions: 1 mmol of nitrile **1a**, 2 equiv of NaN<sub>3</sub>, 1 mL of NMP/AcOH/H<sub>2</sub>O (7:2:1) in a Biotage Initiator (see Section “Microwave and flow instrumentation” for details; only selected data are shown for clarity). The contour plot was generated by a least square fit of the experimental data set assuming a second order rate law ( $dP/dt = k([A]_0 - [P])([B]_0 - [P])$ );  $k = A \cdot e^{-E_a/RT}$ . The best fit was obtained with  $E_a = 67.0$  kJ/mol ( $\sigma E_a = 2.9$  kJ/mol)

benzylic tetrazoles **2b** and **2c** and 5-(2-furanyl)-*1H*-tetrazole **2l** were isolated by liquid–liquid extraction with CHCl<sub>3</sub>/aqueous NaHCO<sub>3</sub> followed by acidification of the aqueous phase with conc. HCl and extraction with EtOAc. The sterically hindered substrates **1o** and **1p** required longer reaction times and the amount of NaN<sub>3</sub> was increased to 4 equiv. The products were isolated by extraction and subsequent precipitation as described above for 5-benzhydryltetrazole **2a**.

Importantly, in the SiC reactor plate heated on a standard hot plate, the 14 tetrazoles **2a–n** were synthesized in parallel in a single experiment, with conversions, product purities, and isolated yields virtually identical to the microwave runs (Table 2, SiC).

The above-described reaction in the NMP/AcOH/H<sub>2</sub>O solvent system could be easily developed into a homogeneous protocol (Table 3, MW). Because of the limited solubility of NaN<sub>3</sub> in H<sub>2</sub>O (417 mg/mL at 17 °C), however, the proportion of H<sub>2</sub>O in the solvent mixture had to be increased to realize the contemplated two-feed concept for continuous flow processing. The increased amounts of water, though, reduced the solubility of the nitrile starting materials and, therefore, the total concentration of the nitrile was reduced to a ~0.69 M solution. Addition of 450 μL of a saturated NaN<sub>3</sub> solution to 1 mmol of nitriles **1a–1n** in 1 mL NMP/AcOH (5:2) produces a roughly 0.69 M solution of the nitriles in a NMP/AcOH/H<sub>2</sub>O (5:2:3) solvent system containing ~2.5 equiv of NaN<sub>3</sub> [31]. Most reaction mixtures remained homogenous upon addition of aqueous NaN<sub>3</sub> to the nitrile solution at room temperature. Only the rather unpolar nitriles **1g**, **1i**, and **1k** (**1k** is not an unpolar nitrile) required some heating (60–80 °C) to prevent precipitation of the nitriles. Gratifyingly, full conversions and high yields of isolated products were also obtained with these less concentrated reaction mixtures after reaction times of 10–15 min at 220 °C in the microwave batch reactor (ca. 18 bar internal pressure, Table 3). The nitriles **1o** and **1p** required too long reaction times and/or too large an excess of NaN<sub>3</sub> and, therefore, attempts to develop a homogeneous protocol for these two substrates were not undertaken.

For the continuous flow reactions, a ~0.9 M solution of the nitriles **1a–n** in NMP/AcOH (5:2) was introduced into the

**Table 2.** Synthesis of 5-substituted-*IH*-tetrazoles **2a–2p** in a microwave batch reactor and a silicon carbide (SiC) reaction block<sup>a</sup>

$$\text{R}^1\text{-CN} \xrightarrow[\text{220 } ^\circ\text{C, 5-30 min}]{\text{NaN}_3 \text{ (2 equiv) NMP/AcOH/H}_2\text{O 7:2:1}} \text{R}^1\text{-C} \begin{matrix} \text{N} \\ \text{N} \\ \text{N} \\ \text{H} \end{matrix}$$

**1**  **2**

	Substrate	$\Delta$	$t^b$ (min)	Yield (%)	Work up <sup>c</sup>		Substrate	$\Delta$	$t^b$ (min)	Yield (%)	Work up <sup>c</sup>
<b>1a</b>		MW	10	85	C	<b>1i</b>		MW	5	92	A
		SiC	15	83	C			SiC	10	94	A
<b>1b</b>		MW	5	94	B	<b>1j</b>		MW	5	90/96	A/B
		SiC	10	97	B			SiC	10	93	A
<b>1c</b>		MW	5	90	B	<b>1k</b>		MW	5	92	A
		SiC	10	88	B			SiC	10	91	A
<b>1d</b>		MW	6	84/95	A/B	<b>1l</b>		MW	5	97	B
		SiC	10	84	A			SiC	10	96	B
<b>1e</b>		MW	5	94/98	A/B	<b>1m</b>		MW	5	77	D
		SiC	10	92	A			SiC	10	79	D
<b>1f</b>		MW	5	97	A	<b>1n</b>		MW	5	69	D
		SiC	10	94	A			SiC	10	69	D
<b>1g</b>		MW	5	98	A	<b>1o</b>		MW	30 <sup>d</sup>	79	C
		SiC	10	97	A			SiC	-	-	-
<b>1h</b>		MW	6	80/88	A/B	<b>1p</b>		MW	30 <sup>d</sup>	86	C
		SiC	10	77	A			SiC	-	-	-

<sup>a</sup>Conditions: 1.0 mmol nitrile, 2.0 mmol  $\text{NaN}_3$ , 1.0 mL solvent (NMP/AcOH/ $\text{H}_2\text{O}$  = 7:2:1); 220 °C. MW: single-mode microwave heating (Biotage Initiator); SiC: hotplate/magnetic stirrer with silicon carbide reactor block.

<sup>b</sup>Reaction times refer to hold times at 220 °C in case of MW experiments (ramp time ~1.5 min, cooling time ~2.5 min), and total heating times for the SiC experiments.

<sup>c</sup>Work-up methods: A: product precipitation 1N HCl (pH 1); B: liquid-liquid extraction with  $\text{CHCl}_3$  followed by acidification with conc. HCl and extraction with EtOAc; C: liquid-liquid extraction with toluene followed by product precipitation with conc. HCl; D: liquid-liquid extraction with  $\text{CHCl}_3$  followed by pH adjustment with conc. HCl to pH 5.

<sup>d</sup>4.0 equiv of  $\text{NaN}_3$ , 1.5 mL solvent.

Uniqsis flow reactor (Figure 2) equipped with a 10-mL silicon-coated stainless-steel coil (Sulfinert<sup>®</sup>; i.d. 1.0 mm) [32] via the first pump (feed A). The saturated (ca. 5.2 M) solution of  $\text{NaN}_3$  in  $\text{H}_2\text{O}$  was fed in the reactor by the second pump. The two feeds

were combined in a T-mixer at room temperature at flow rates of, respectively, 0.69 and 0.31 mL/min (0.45 and 0.21 mL/min for substrate **1a**). For the nitriles **1g**, **1i**, and **1k**, a 2-mL glass static mixer heated to 150 °C was used instead of the T-mixer to

**Table 3.** Synthesis of 5-substituted-*IH*-tetrazoles **2a–2n** in a microwave batch reactor and a continuous flow reactor under homogeneous conditions<sup>a</sup>

$$\text{R}^1\text{-CN} \xrightarrow[\text{220 } ^\circ\text{C, 10-15 min}]{\text{NaN}_3 \text{ (2.5 equiv) NMP/AcOH/H}_2\text{O 5:2:3}} \text{R}^1\text{-C} \begin{matrix} \text{N} \\ \text{N} \\ \text{N} \\ \text{H} \end{matrix}$$

**1**  **2**

	$\Delta$	Time <sup>b</sup> (min)	Yield <sup>c</sup> (%)	Work-up <sup>d</sup>		$\Delta$	Time <sup>b</sup> (min)	Yield <sup>c</sup> (%)	Work-up <sup>d</sup>
<b>1a</b>	MW	15	81	C	<b>1h</b>	MW	10	84	A
	flow <sup>e</sup>	15	82	C		flow	10	87	A
<b>1b</b>	MW	10	97	B	<b>1i</b>	MW	10	97	A
	Flow	10	94	B		flow	10	97	A
<b>1c</b>	MW	10	87	B	<b>1j</b>	MW	10	93	A
	Flow	10	92	B		flow	10	97	A
<b>1d</b>	MW	10	86	A	<b>1k</b>	MW	10	87	A
	Flow	10	95	A		flow	10	89	A
<b>1e</b>	MW	10	96	A	<b>1l</b>	MW	10	97	B
	Flow	10	98	A		flow	10	98	B
<b>1f</b>	MW	10	90	A	<b>1m</b>	MW	10	71	D
	Flow	10	90	A		flow	10	75	D
<b>1g</b>	MW	10	98	A	<b>1n</b>	MW	10	62	D
	Flow	10	96	A		flow	10	68	D

<sup>a</sup>Conditions MW: 1.0 mmol nitrile **1**, 2.5 mmol  $\text{NaN}_3$ , 1.5 mL solvent (NMP/AcOH/ $\text{H}_2\text{O}$  = 5:2:3). Single-mode microwave heating at 220 °C (Biotage Initiator). Flow conditions: feed A (~0.9 M solution of nitrile in 5:2 NMP/AcOH) at a flow rate of 0.69 mL/min and feed B (~5.2 M  $\text{NaN}_3$  in  $\text{H}_2\text{O}$ ) at 0.31 mL/min at 220 °C (FlowSyn, Uniqsis Ltd).

<sup>b</sup>Reaction times refer to hold times at 220 °C in case of MW experiments (ramp time ~2 min, cooling time ~2 min), and residence times in the 10 mL heated coil for flow experiments.

<sup>c</sup>Isolated product yields for the flow experiments refer to steady state yields (see Experimental Section for details).

<sup>d</sup>For work-up, see Table 2 footnote c.

<sup>e</sup>0.45 mL/min feed A and 0.21 mL/min feed B (residence time 15 min).

prevent precipitation of the nitriles upon mixing. The combined mixture contained around 2.5 equiv of  $\text{NaN}_3$ . The maximum initial concentration of  $\text{HN}_3$  was around 1.6 M (~7% by weight) and, thus, far below the published safety limit of 20%. The combined stream passed through the 10 mL coil reactor heated to 220 °C and left the reactor through the HE and the BPR (34 bar). The post-reaction mixture could be flowed directly into a beaker with aqueous  $\text{NaNO}_2$  to destroy any excess of  $\text{HN}_3$  [33]. The pure tetrazole products **2d–2k** were isolated via precipitation by simple acidification of the aqueous solution, while the other tetrazoles were isolated by extractive work-up as described above. Product yields and purities were basically identical to those obtained under microwave batch conditions (Table 3, flow).

For the continuous flow high-temperature azide–nitrile addition, a major concern was the choice of a suitable reactor coil material. In general, for reactions involving azides, the entire equipment should be free of heavy metals, such as Cu, since these metals readily form insoluble, explosive heavy-metal azide salts [2].  $\text{HN}_3$  is both a strong oxidant ( $E^\circ = 1.96$  V) and, in the presence of oxidants, a strong reducing agent ( $E^\circ = -3.09$  V), and it dissolves metals such as Fe, Zn, Mn, and Cu [34]. Iron nitrides are formed from  $\text{HN}_3$  and Fe metal at temperatures around 100 °C [35]. A stainless-steel reactor contains a range of metals and the particularly high surface-to-volume ratio in a microstructured reactor may entail pronounced reactor wall effects and unexpected/undesired side and degradative reactions. Tube reactors made out of polytetrafluoroethylene (PTFE) or related materials also appear unsuitable for these transformations, as PTFE possesses very limited pressure resistance at higher temperatures and, further, it is rather permeable to gases [36].

Our initial attempts to perform the high-temperature (220 °C) azide–nitrile cycloaddition reaction in a resistance-heated stainless-steel microtubular flow reactor (ThalesNano X-Cube Flash) indeed failed [37]. Instead of the anticipated tetrazole **2a**, the major product observed by HPLC-UV monitoring was diphenylmethane. We initially speculated that the observed problems were somehow connected to an incompatibility of  $\text{HN}_3$  with the stainless steel of the reactor, but subsequently discovered that the pure tetrazole product, when subjected to the reaction conditions, rapidly decomposed in the used flow reactor. Detailed mechanistic investigations have demonstrated that this degradation starts with an *N*-acetylation of the tetrazole nucleus by AcOH present in the reaction medium [37]. Through a series of subsequent transformations (Huisgen reaction), diphenylacetic acid and ultimately diphenylmethane is formed [37]. Remarkably, none of these degradation products were observed in the actual tetrazole synthesis or by exposing the pure tetrazole to the same reaction conditions (220 °C, 15 min) in a microwave batch reactor [37]. The fast degradation of the tetrazole products in the resistance-heated steel reactor was, however, not related to the steel material but apparently to the particular heating mechanism of this reactor (direct Joule heating of the coil) [37]. In fact, the reaction with diphenylacetone nitrile **1a** as substrate was repeated in a conventional 20-mL stainless-steel coil (1 mm i.d.) on the Uniqsis FlowSyn reactor and the tetrazole product **2a** was isolated in yields and purities identical to those obtained in the passivated coil. Most likely, uneven temperature distributions and the formation of hot spots along the resistance-heated coil at these high temperatures were responsible for the observed degradation [37].

Using the Uniqsis FlowSyn setup, we were even able to increase the temperature to 260 °C for the  $\text{HN}_3$  addition to benzonitrile (**1d**) as substrate. The required residence time was thereby reduced to only 2.5 min. The nitrile solution and an aqueous  $\text{NaN}_3$  stream were continuously introduced into the reactor for 1 h. At flow rates of 2.75 and 1.25 mL/min, respectively, 165 mL of a roughly 0.9 M nitrile solution and 75 mL

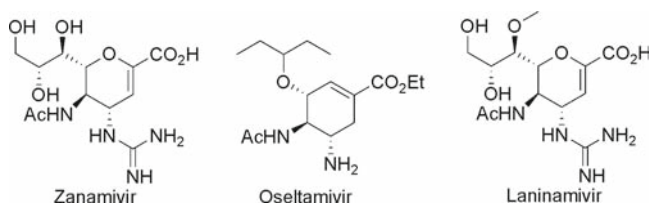
of saturated aqueous  $\text{NaN}_3$  were consumed [31]. The combined stream passed through the 10-mL steel reactor at a total flow rate of 4 mL/min and the steady-state product stream was collected directly in a well-stirred 1-L flask containing  $\text{NaNO}_2$  (242 mmol) in water (550 mL) [13]. The pH of the solution was then adjusted to ~1 with conc. HCl (caution: gas evolution!) and the precipitate collected by filtration to furnish 18.9 g (89%) HPLC-UV and  $^1\text{H-NMR}$  pure (>98%) 5-phenyl-1*H*-tetrazole (**2d**). In principle, the chemical quench step with  $\text{NaNO}_2$  can also be performed inline as the reaction mixture remains homogeneous upon addition of aqueous  $\text{NaNO}_2$  [38]. Therefore, the aqueous  $\text{NaNO}_2$  is fed into the product stream and the combined stream then directly passed into aqueous HCl. Any excess of  $\text{HN}_3$  will decompose and 5-phenyl-1*H*-tetrazole (**2d**) precipitates from the aqueous mixture.

It should be mentioned that a recently published protocol for the flow synthesis of 5-substituted-1*H*-tetrazoles from nitriles and  $\text{NaN}_3$  in NMP/ $\text{H}_2\text{O}$  (9:1) appears not to require any acidic additive or catalyst [38]. Only 1.05 equiv of  $\text{NaN}_3$  was employed to synthesize various tetrazoles in a tubular flow reactor made of perfluoroalkoxy polymer (PFA). A 0.2 M solution of the nitriles in NMP/ $\text{H}_2\text{O}$  containing the azide was pumped through a PFA coil reactor (120  $\mu\text{L}$ ) heated to 190 °C at flow rates of 6  $\mu\text{L}/\text{min}$  (20 min residence time) and the tetrazole products were generally isolated in excellent yields.

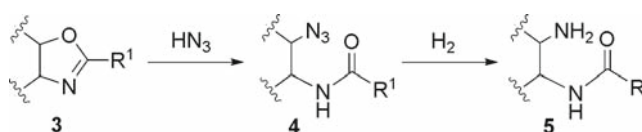
### 2.3. Ring Opening of 2-Oxazolines with Hydrazoic Acid.

The  $\text{S}_{\text{N}}2$  ring opening of oxazolines **3** with an azide source is a key step in the synthesis of neuraminic acid analogues (e.g., neuraminidase inhibitors, such as Zanamivir and Oseltamivir, Figure 6) [39, 40]. Under basic conditions, 2-oxazolines are virtually impervious to nucleophiles and, thus, the oxazoline nucleus becomes a popular protecting and/or directing group in organic synthesis [41]. In the presence of acids, however, oxazolines are quite susceptible to nucleophilic ring opening [40–42]. The  $\text{S}_{\text{N}}2$  attack of  $\text{N}_3^-$  generally occurs at the ether carbon C5 of the ring and leads to the *N*-(2-azidoethyl)acylamide scaffold **4** (Figure 7). The reaction is usually performed with  $\text{TMSN}_3$  in a high boiling alcohol, such as *t*-BuOH [40–42]. The introduced azide can be reduced afterward to furnish monoacylated diamines of type **5**. Selectively acylated 1,2-diamines are often difficult to produce by other means and even monoacylation of symmetrical diamines presents a challenge due to the tendency for bisacylation [43].

For the first reported synthesis of Zanamivir on scale, the stereospecific ring-opening reaction of the corresponding oxazoline intermediate to introduce the amino group at C4 was performed with  $\text{TMSN}_3$  in *t*-BuOH as solvent at 80 °C within



**Figure 6.** Neuraminidase inhibitors used or researched for the treatment and prophylaxis of influenza



**Figure 7.** Two-step synthesis of selectively monoacylated 1,2-diamines **5** starting from 2-oxazolines **3**

10.5 h on up to a 600-g scale [40c]. However,  $\text{TMSN}_3$  quickly releases  $\text{HN}_3$  in protic solvents and  $\text{HN}_3$  can be detected in the headspace above the  $\text{TMSN}_3$  solution immediately upon mixing with protic solvents (Figure 8) [44]. Batch protocols of this type can therefore be considered to be extremely hazardous.

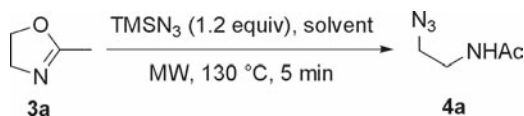
In fact,  $\text{HN}_3$  is the actual reagent in this ring opening and the reaction generally does not proceed with neat  $\text{TMSN}_3$  or  $\text{TMSN}_3$  in aprotic solvents [42c]. In our hands, MeOH was the best solvent for this reaction. The structurally very simple and commercially available 2-methyl-2-oxazoline **3a** was fully converted to the desired azide with 1.2 equiv of  $\text{TMSN}_3$  after 5 min at 130 °C in MeOH as the solvent in a batch microwave reactor (8 bar internal pressure) (Table 4). The ring opening was considerably slower in *i*-PrOH or *t*-BuOH as the solvent, and, as expected, the reaction did not work at all in aprotic solvents, such as tetrahydrofuran (THF) and MeCN. In aqueous reaction media, 2-oxazolines tend to hydrolyze via a nucleophilic reaction at the 2-position [41] and, thus, a strategy as described above for the synthesis of 5-substituted tetrazoles with  $\text{NaN}_3$  in a  $\text{H}_2\text{O}/\text{acid}$  solvent mixture appeared unsuitable and was not attempted.

Virtually, no byproducts were generated in this reaction, and the H-NMR/GC-FID-pure azide **4a** was isolated in almost quantitative yield after simple evaporation of the solvent and any excess of reagent. Importantly, a direct progression to a subse-



**Figure 8.**  $\text{HN}_3$  can be detected by a filter paper impregnated with  $\text{FeCl}_3$ . The color of the paper immediately turns into red upon contact with the headspace of the vial filled with  $\text{TMSN}_3$  and MeOH (left vial; right vial is an empty vial for comparison) [44]

**Table 4.** Solvent screening for the ring-opening of 2-Methyl-2-oxazoline (**3a**)<sup>a</sup>



Solvent	Conv.(%)	Solvent	Conv.(%)
MeOH	100	MeCN	0
<i>i</i> -PrOH	92	THF	0
<i>t</i> -BuOH	50		

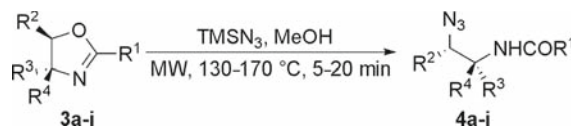
<sup>a</sup>GC-FID conversions, conditions: 5 min at 130 °C (Biotage Initiator 2.5), 1.8 mmol 2-methyl-2-oxazoline (**3a**), 300  $\mu\text{L}$  solvent, 1.2 equiv  $\text{TMSN}_3$ .

quent hydrogenation without isolation of the intermediate azide should thus be possible. Similar results were obtained with 2-ethyl-2-oxazoline **3b**. The 2-phenyl derivative **3c** required somewhat higher reaction temperatures and the reaction time was prolonged to 10 min. Full conversions of the 4-substituted 2-methyl oxazolines **3d** and **3e** were achieved after 10 min at 130 °C. With the 4,5-disubstituted oxazolines **3f** and **3g**, 1.3 equiv of  $\text{TMSN}_3$  were required to complete the reaction within 10 min at 140 °C (Table 5).

With 4,4-dimethyl-substituted oxazolines **3h** and **3i**, the reaction was surprisingly slow under these conditions. Oxazoline **3h** required 25 min at 160 °C for conversions >90% with 1.2 equiv of  $\text{TMSN}_3$  and considerable amounts of side products were detectable by GC-FID. The phenyl-substituted derivative **3i** was even less reactive. For example, with 1.3 equiv of  $\text{TMSN}_3$ , after 35 min at 160 °C, conversions of merely 27% were obtained and impurities started to emerge (GC-FID). To obtain reasonable reaction rates for these substrates, a range of different acidic catalysts were screened to activate the oxazoline ring. In particular, hard, oxophilic Lewis acids and Brønsted acids accelerated the reaction efficiently, but, unfortunately, the purity of the reaction generally decreased in the presence of an acid (Table 6).

We have also discovered that catalytic amounts of *N*-iodo- and *N*-bromosuccinimide increased the reaction rate significantly (Table 7). Presumably, the oxazoline ring is halogenated and the susceptibility for the nucleophilic ring opening is thus increased.  $\text{I}^+$  (or  $\text{Br}^+$ ) may then be transferred from the formed *N*-halogenoamide to the solvent (or any other nucleophile in the mixture) and a further catalytic cycle starts (Scheme 2). However, very explosive iodo- or bromoazide may be formed during the reaction and therefore this strategy was not pursued further.

**Table 5.** Synthesis of *N*-(2-azidoethyl)acylamides **4a–4i** under microwave batch conditions<sup>a</sup>



	Substrate	Time (min)	Temp. (°C)	$\text{TMSN}_3$ (equiv)	Yield (%) <sup>b</sup>
<b>3a</b>		5	130	1.2	97
<b>3b</b>		5	130	1.2	99
<b>3c</b>		10	140	1.2	96
<b>3d</b>		10	130	1.2	90
<b>3e</b>		10	130	1.2	96
<b>3f</b>		10	140	1.3	95
<b>3g</b>		10	140	1.3	88
<b>3h</b>		15	160	1.3	87 <sup>c</sup>
<b>3i</b>		20	170	1.3	69 <sup>c</sup>

<sup>a</sup>Conditions: 1.8 mmol of oxazoline **3**, 1.2–1.3 equiv  $\text{TMSN}_3$ , 300  $\mu\text{L}$  of MeOH, single-mode microwave reactor (Biotage Initiator).

<sup>b</sup>Products **4a** and **4b** were isolated by removing the solvent and excess of reagent under reduced pressure; **4c–4i** were further purified by extraction with 0.5 N HCl/ $\text{CHCl}_3$ .

<sup>c</sup>10 mol% TEA was used as catalyst.

**Table 6.** Catalyst screening for the ring opening of oxazoline **3h**<sup>a</sup>

Cat	Conv. (%)	cat	Conv. (%)
No cat	36	10% BF <sub>3</sub>	53
10% Pd(OAc) <sub>2</sub>	35	10% Bu <sub>3</sub> SnO	78
10% Cu(OTf) <sub>2</sub>	75	10% TMSCl	88
10% Zn(OTf) <sub>2</sub>	85	10% MSA	74
10% Yb(OTf) <sub>3</sub>	94	10% TFA	70

<sup>a</sup>GC-FID conversions, conditions: 160 °C, 10 min (Biotage Initiator 2.5); 1.8 mmol 2,2,4-trimethyloxazoline **3h**, 200 μL MeOH, 1.2 equiv TMSN<sub>3</sub>.

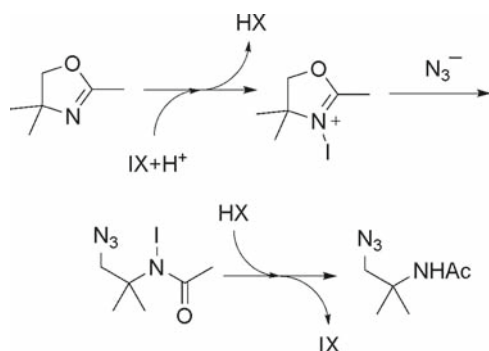
**Table 7.** Catalyst screening for the ring opening of oxazoline **3h**<sup>a</sup>

Catalyst (mol%)	Conv (%)	Catalyst (mol%)	Conv (%)
NIS (6)	96 <sup>b</sup>	NBS (5)	85
NIS (3)	76	NBS (3)	80

<sup>a</sup>GC-FID conversions, conditions: 160 °C, 10 min (Biotage Initiator 2.5); 1.8 mmol 2,2,4-trimethyloxazoline **3h**, 200 μL MeOH, 1.2 equiv TMSN<sub>3</sub>.

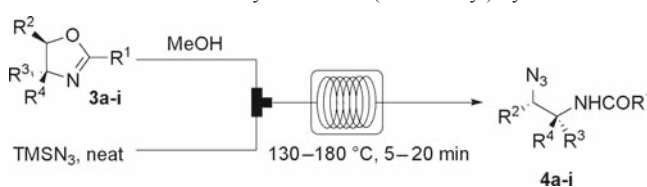
<sup>b</sup>The product was isolated in 80% product yield after extraction with CHCl<sub>3</sub>/sat. NaHCO<sub>3</sub>.

**Scheme 2.** Possible mechanism for the NIS (or NBS)-catalyzed ring opening. X<sup>-</sup> in the scheme may be any nucleophile present in the reaction mixture.



Ultimately, we discovered that the reaction is 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<sub>3</sub> from TMSN<sub>3</sub> in this rather concentrated mixture (1.8 mmol 2,2,4-trimethyloxazoline **3h**, 200 μL MeOH, and 1.3 equiv of TMSN<sub>3</sub>). The azides **4a** and **4b** could be isolated by simple evaporation of the solvent, whereas azides **4c–4i** were further purified by extraction with 0.5 N HCl/CHCl<sub>3</sub> to give products with high purity (>99% by GC-FID and <sup>1</sup>H NMR spectroscopy, Table 5).

Although the microwave batch reactions were performed with fairly concentrated solutions of the oxazoline substrates (1.8 mmol oxazoline **3a–3i**, 200–300 μL MeOH, and 1.2–1.3 equiv TMSN<sub>3</sub>), all reaction mixtures **3a–3i** were homogeneous. Therefore, the microwave batch protocol could be directly translated to a continuous flow format without any re-optimization of the batch conditions (Uniqsis FlowSyn, Figure 2). Hence, 2.5–4 M solutions of the oxazoline starting materials in MeOH were pumped into the reactor via feed A. TMSN<sub>3</sub> was fed into the reactor as the neat reagent via the second pump (feed B). For a quick proof-of-concept study, we introduced 2 mL of the oxazoline solutions into the FlowSyn reactor equipped with a 20-mL stainless-steel coil (1.0 mm i.d.). The two streams, A and B, were mixed in a T-mixer at room temperature at appropriate flow rates, so that the desired excess of TMSN<sub>3</sub> is established in the combined stream and so that the residence time in the coil reactor corresponds to the reaction time in the microwave batch experiments. After passing the coil reactor, the reaction mixture was cooled in a plate HE to room temperature, and it left the reactor through a 34 bar BPR. A 52 bar BPR was used

**Table 8.** Continuous flow synthesis of *N*-(2-azidoethyl)acylamides<sup>a</sup>

	Flow rate A/B (mL/min)	Conc. Feed A (M)	Time (min)	Temp (°C)	TMSN <sub>3</sub> (equiv)	Yield (%) <sup>b</sup>
<b>1a</b>	2.45/1.55	4.0	5	130	1.2	93
<b>1b</b>	2.45/1.55	4.0	5	130	1.2	95
<b>1c</b>	1.25/0.75	3.8	10	140	1.2	94
<b>1d</b>	1.35/0.65	3.05	10	140	1.2	74
<b>1e</b>	1.35/0.65	3.05	10	140	1.2	91
<b>1f</b>	1.40/0.60	2.5	10	150	1.3	91
<b>1g</b>	1.25/0.75	3.5	10	150	1.3	67
<b>1h</b>	0.80/0.50	3.65	15.4	170	1.3	77 <sup>c</sup>
<b>1i</b>	0.70/0.30	2.5	20	180	1.3	59 <sup>c</sup>

<sup>a</sup>Conditions: feed A: 2 mL of the oxazoline solutions; feed B: neat TMSN<sub>3</sub>; reaction times refer to residence times in the heated coil reactor (20 mL, stainless steel, 34 or 52 bar back-pressure regulator for reactions above 150 °C).

<sup>b</sup>For work-up, see Table 5 footnote b.

<sup>c</sup>10 mol% TEA was used as catalyst.

for reactions above 150 °C. The complete post-reaction mixture was collected (plus 5 mL pre- and 10 mL post-collection) and analyzed by GC-FID, and the *N*-(2-azidoethyl)acylamides **4a–4i** were isolated as described above (Table 8). The conversions obtained in the flow reactions were slightly lower than those obtained under batch microwave conditions. This can be mainly attributed to longitudinal dispersion of the introduced reaction plug [45]. Dispersion causes the plug to broaden as it moves down the reactor and the reaction mixture becomes less concentrated [45]. To obtain better conversions, the reaction temperatures were increased for the substrates **3d–3i**. It should be noted that this issue will not arise when the reactor is operated continuously or can be circumvented by “steady-state collection” (see tetrazole synthesis above).

To demonstrate this point, the flow reaction was repeated on a 10-fold scale without changing or re-optimizing the reaction parameters with oxazoline **3h** as substrate. A 3.65 M solution of oxazoline **3h** in MeOH (20 mL total volume) and neat TMSN<sub>3</sub> were fed continuously into the reactor for 25 min at flow rates of 0.80 and 0.50 mL/min, respectively. A volume of 12.5 mL of TMSN<sub>3</sub> was consumed during this process, corresponding to 1.3 equiv of HN<sub>3</sub>. After the combined reaction mixture had passed the 20-mL coil reactor heated at 170 °C at a total flow rate of 1.30 mL/min, the stream left the reactor through the HE and a 54 bar BPR. Again, the complete reaction mixture was collected and the dimethyl-substituted *N*-(2-azidoethyl)acylamide **4h** was isolated in 84% product yield (9.6 g).

The *N*-(2-azidoethyl)acylamides **4** obtained in the oxazoline ring opening can subsequently be directly hydrogenated using continuous flow hydrogenation technology, either using the isolated and purified azides, or the crude material resulting from the HN<sub>3</sub> ring-opening step. Importantly, the hydrogenation event destroys any excess of HN<sub>3</sub> in the system. The results of these investigations are detailed in our previous publication [12]. TMSN<sub>3</sub> does not interfere with the hydrogenation reaction on this scale (2 mmol substrate) and, important from a safety standpoint, no HN<sub>3</sub> was detectable in the reaction mixtures after the reduction [12].

### 3. Conclusion

In conclusion, we have developed two fast and efficient high-temperature protocols for two synthetic transformations of significant industrial interest using hydrazoic acid as



the reagent. The first reaction involved the addition of  $\text{HN}_3$  to nitriles to afford 5-substituted-1*H*-tetrazoles, while the second reaction furnished the *N*-(2-azidoethyl)acylamide scaffold by a ring-opening reaction of 2-oxazolines with  $\text{HN}_3$ . Even though  $\text{HN}_3$  is a very explosive compound, the reactions could be performed at remarkably high temperatures in sealed-vessel microwave batch equipment. The desired products were formed after short reaction times and isolated in excellent yields and purities applying simple work-up procedures. However, although dedicated batch microwave reactors (or other autoclave-type reactors) are useful tools for a rapid screening of reaction conditions or for synthesizing compound libraries, this batch methods are clearly not suitable for reactions on scale, because of the safety issues associated with  $\text{HN}_3$ . Therefore, a continuous flow process in a microstructured flow device was envisaged from the outset of our investigations. The very characteristics of microreactors, such as small volumes, and high pressure and temperature capabilities, make this technology ideal for high-temperature chemistry or for reactions involving volatile and/or explosive reagents. Owing to a lack of a reactor headspace, the risk of a  $\text{HN}_3$  explosion is significantly reduced. Furthermore, the available concentration of  $\text{HN}_3$  should in fact be significantly higher than that in a sealed microwave vessel, where a large amount of this volatile reagent can be expected to be in the gas phase. The generation and secure handling of hazardous  $\text{HN}_3$  in a microreactor environment as described herein may be valuable for many further reactions involving this versatile reagent.

## 4. Experimental

**4.1. General Experimental Conditions.**  $^1\text{H}$ -NMR spectra were recorded on a Bruker 300 MHz instrument.  $^{13}\text{C}$ -NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts ( $\delta$ ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Low-resolution mass spectra were obtained on a LC-MS instrument using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) in positive or negative mode (Agilent 1100 LC/MS or Shimadzu LCMS-2020). GC-FID analysis was performed on a Trace-GC (ThermoFisher) with a flame ionization detector using a HP5 column (30 m  $\times$  0.250 mm  $\times$  0.025  $\mu\text{m}$ ). After 1 min at 50  $^\circ\text{C}$ , the temperature was increased in 25  $^\circ\text{C}$  per minute steps up to 300  $^\circ\text{C}$  and kept at 300  $^\circ\text{C}$  for 4 min. The detector gas for the flame ionization was  $\text{H}_2$  and compressed air (5.0 quality). GC-MS spectra were recorded using a Thermo Focus GC coupled with a Thermo DSQ II (EI, 70 eV). A HP5-MS column (30 m  $\times$  0.250 mm  $\times$  0.025  $\mu\text{m}$ ) was used with helium as carrier gas (1 mL/min constant flow). The injector temperature was set to 280  $^\circ\text{C}$ . After 1 min at 50  $^\circ\text{C}$ , the temperature was increased in 25  $^\circ\text{C}$  per minute steps up to 300  $^\circ\text{C}$  and kept at 300  $^\circ\text{C}$  for 4 min. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150  $\times$  4.6 mm, particle size 5  $\mu\text{m}$ ) at 25  $^\circ\text{C}$  using mobile phases A (water/acetonitrile, 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. TLC analyses were performed on pre-coated (silica gel 60 HF254) plates. Melting points were determined on a Stuart<sup>TM</sup> SMP3 melting point apparatus. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification.

**4.2. Microwave and Flow Instrumentation.** Microwave-assisted synthesis was carried out in a Biotage Initiator 8 EXP 2.5 single-mode microwave instrument producing controlled

irradiation at 2.450 GHz. Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel. Flow chemistry experiments were performed in a Uniqsis FlowSyn reactor in standard configuration [15].

**4.3. General Experimental Procedure for Tetrazole Synthesis Under Microwave Conditions (2a–2p, Table 2).** Into a 5 mL microwave process vial equipped with a magnetic stir bar were placed 1.0 mmol of the respective nitrile **1a–1p**, 2.0 mmol of  $\text{NaN}_3$  (2 equiv, 130 mg), and 1.0 mL of NMP/AcOH/ $\text{H}_2\text{O}$  (7:2:1) (v/v/v). The vials were sealed by capping with a Teflon septum fitted in an aluminum crimp top, and the samples were irradiated in a Biotage Initiator 8 EXP 2.5 for 5 min at 220  $^\circ\text{C}$  ( $\sim$ 7 bar). After the reaction time has elapsed, the mixtures were cooled to 45  $^\circ\text{C}$  by compressed air. *Caution:* Residual pressure (up to  $\sim$ 3 bar) should be released before opening the vessel by carefully penetrating the septum with a needle in a fume hood. Work-up A: The reaction mixture was added dropwise into a solution of 1.0 mmol  $\text{NaNO}_2$  in  $\sim$ 10 mL of  $\text{H}_2\text{O}$  (*caution:* gas evolution). The pH of the solution was adjusted to  $\sim$ 1 with conc. HCl (*caution:* gas evolution). The mixture was cooled in an ice bath, and the precipitate collected by filtration and washed thoroughly with cold 1 N HCl to furnish the pure (HPLC at 215 nm  $>$ 99%) tetrazole products (Table 2). Work-up B: The reaction mixture was poured into 10 mL of saturated  $\text{NaHCO}_3$  and extracted 3 times with 20 mL of  $\text{CHCl}_3$ .  $\text{NaNO}_2$  (1.0 mmol) was added to the aqueous phase and the solution was carefully acidified with conc. HCl to pH  $\sim$ 1 (*caution:* gas evolution) and extracted 3 times with 20 mL of EtOAc. The combined organic phases were dried over magnesium sulfate and concentrated in vacuo to obtain the pure (HPLC at 215 nm,  $>$ 99%) tetrazole products (Table 2). Work-up C: The reaction mixture was poured into 20 mL of saturated  $\text{NaHCO}_3$  and subsequently extracted with 10 mL of toluene to remove unreacted nitrile.  $\text{NaNO}_2$  (1.0 mmol) was added to the aqueous phase and the solution was carefully acidified with conc. HCl to pH  $\sim$ 1 (*caution:* gas evolution). The solution was cooled in an ice bath, and the precipitate collected by filtration and washed thoroughly with cold 1 N HCl to furnish the desired pure tetrazole products (HPLC at 215 nm  $>$ 99%) (Table 2). Work-up D: The amphoteric products **2m** and **2n** were isolated by adding 2 mL of saturated  $\text{NaHCO}_3$  to the reaction mixture followed by three extractions with 8 mL of  $\text{CHCl}_3$ .  $\text{NaNO}_2$  (1 mmol) was added to the aqueous phase and the solution was carefully acidified with conc. HCl to pH  $\sim$ 5 (*caution:* gas evolution). The mixture was cooled, filtered, and washed with cold water (pH  $\sim$ 4) to provide pure tetrazole products (HPLC at 215 nm,  $>$ 99%) (Table 2).

**4.4. General Experimental Procedure for Tetrazole Synthesis Using the FlowSyn Reactor (2a–2n, Table 3).** Nitrile (9.0 mmol) was dissolved in 9.0 mL NMP/AcOH (5:2) in a graduated cylinder (feed A,  $\sim$ 0.9 M) and 1688.9 mg of  $\text{NaN}_3$  was dissolved in 4.05 mL  $\text{H}_2\text{O}$  (feed B;  $\sim$ 5.2 M,  $\sim$ 29% by weight). Diphenylacetonitrile **1a** in NMP/AcOH solution was filtered before flow processing (the used technical grade diphenylacetonitrile contained fine metallic debris). The streams A and B were mixed together at flow rates of 0.69 and 0.31 mL/min, respectively (0.45 and 0.21 mL/min for nitrile **1a**) in a T-mixer at room temperature (providing  $\sim$ 2.5 equiv  $\text{NaN}_3$ ) and the resulting stream (1.0 mL/min) was passed through the Sulfinert<sup>®</sup> reactor coil ( $\sim$ 10 mL heated volume, 10 min residence time for nitriles **1b–1n**, and 15 min residence time for nitrile **1a**) at 220  $^\circ\text{C}$ . The two streams were switched via a switching valve from pure solvent to reagent when the reactor was stable. Stream B was switched with a delay to ensure that both reagents arrive at the T-mixer at the same time. After passing

the coil reactor, the mixtures were cooled in the plate HE to room temperature, and they left the reactor through a 500 psi (~34 bar) BPR. For the nitriles **1g**, **1i**, and **1k**, the two feeds A and B were combined in a 2 mL glass static mixer heated to 150 °C to prevent precipitation of the nitriles upon mixing. No HE was used for these reactions. The leading (~1.4 mL) and trailing ends of the reaction plug were rejected, and only the steady-state reaction product was collected to establish the steady-state yield. Therefore, the product was collected for 8 min in a graduated cylinder and isolated as described above. Yields in percent were calculated from the collected volume and the flow rate under the assumption that the volume does not change after mixing of the two streams and during the reaction (Table 3).

**5-Benzhydryltetrazole (2a).** Yellowish solid, mp 165–166 °C, lit. [25e] mp 164–165 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 16.45 (br s, 1H, NH), 7.38–7.25 (m, 10H, aromatic), 5.96 (s, 1H, CH); MS (neg-APCI): *m/z* (%): 235 (100) [M – H]<sup>–</sup>.

**5-Benzyltetrazole (2b).** Colorless solid, mp 123–124 °C, lit. [26c] mp 121–122 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 7.36–7.34 (m, 2H, aromatic), 7.28–7.26 (m, 3H, aromatic), 4.29 (s, 2H, CH<sub>2</sub>); MS (neg-APCI): *m/z* (%): 159 (100) [M – H]<sup>–</sup>.

**5-(4'-Chlorophenyl)methyltetrazole (2c).** Colorless solid, mp 160–162 °C, lit. [46] mp 164 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 7.40 (d, <sup>3</sup>*J*(H,H) = 8.4 Hz, 2H, aromatic), 7.30 (d, <sup>3</sup>*J*(H,H) = 8.4 Hz, 2H, aromatic), 4.30 (s, 2H, CH<sub>2</sub>); MS (neg-APCI): *m/z* (%): 193 (100) [M – H]<sup>–</sup>, 159 (15) [M – Cl]<sup>–</sup>.

**5-Phenyltetrazole (2d).** Colorless solid, mp 217–218 °C, lit. [22a] mp 215–216 °C with decomp.; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 16.31 (br s, 1H, NH), 8.06–8.03 (m, 2H, aromatic), 7.65–7.59 (m, 3H, aromatic); MS (neg-APCI): *m/z* (%): 145 (100) [M – H]<sup>–</sup>, 117 (33) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(4'-Tolyl)tetrazole (2e).** Colorless solid, mp 251–252 °C, lit. [26f] mp 246–248 °C with decomp.; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 7.93 (d, <sup>3</sup>*J*(H,H) = 8.0 Hz, 2H, aromatic), 7.41 (d, <sup>3</sup>*J*(H,H) = 8.0 Hz, 2H, aromatic), 2.38 (s, 3H, CH<sub>3</sub>); MS (neg-APCI): *m/z* (%): 159 (100) [M – H]<sup>–</sup>, 131 (28) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(3'-Methoxyphenyl)tetrazole (2f).** Colorless solid, mp 158–160 °C, lit. [26c] mp 156–157 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 7.64–7.59 (m, 2H, aromatic), 7.52 (t, <sup>3</sup>*J*(H,H) = 8.0 Hz, 1H, aromatic), 7.16 (dd, *J*(H,H) = 2.4, 8.1 Hz, 1H, aromatic), 3.85 (s, 3H, CH<sub>3</sub>); MS (neg-APCI): *m/z* (%): 175 (100) [M – H]<sup>–</sup>, 147 (23) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(4'-Chlorophenyl)tetrazole (2g).** Colorless solid, mp 252–254 °C with decomp., lit. [26f] mp 252–254 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 8.05 (d, <sup>3</sup>*J*(H,H) = 8.4 Hz, 2H, aromatic), 7.69 (d, <sup>3</sup>*J*(H,H) = 8.4 Hz, 2H, aromatic); MS (neg-APCI): *m/z* (%): 179 (100) [M – H]<sup>–</sup>, 151 (33) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(2'-Chlorophenyl)tetrazole (2h).** Colorless solid, mp 179–181 °C with decomp., lit. [28b] mp 173–175 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 7.83–7.80 (m, 1H, aromatic), 7.73–7.70 (m, 1H, aromatic), 7.66–7.53 (m, 2H, aromatic); MS (neg-APCI): *m/z* (%): 179 (100) [M – H]<sup>–</sup>, 151 (38) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(4'-Bromophenyl)tetrazole (2i).** Brownish solid, mp 268–269 °C with decomp., lit. [21a] mp 271–273 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 7.98 (d, <sup>3</sup>*J*(H,H) = 8.4 Hz, 2H, aromatic), 7.82 (d, <sup>3</sup>*J*(H,H) = 8.4 Hz, 2H, aromatic); MS (neg-ESI): *m/z* (%): 225 (100) [M – H]<sup>–</sup>, 197 (21) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(4'-(Trifluoromethyl)phenyl)tetrazole (2j).** Colorless solid, mp 222–223 °C with decomp., lit. [26f] mp 221–222 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 8.26 (d, <sup>3</sup>*J*(H,H) = 8.1 Hz, 2H, aromatic), 7.98 (d, <sup>3</sup>*J*(H,H) = 8.1 Hz, 2H, aromatic); MS (neg-APCI): *m/z* (%): 213 (100) [M – H]<sup>–</sup>, 185 (24) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(3'-Nitrophenyl)tetrazole (2k).** Yellowish solid, mp 118–120 °C with decomp., lit. [25e] mp 145–146 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 8.82 (s, 1H, aromatic), 8.47–

8.40 (m, 2H, aromatic), 7.90 (t, <sup>3</sup>*J*(H,H) = 8.1 Hz, 1H, aromatic); MS (neg-APCI): *m/z* (%): 190 (100) [M – H]<sup>–</sup>, 162 (44) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(2'-Furyl)tetrazole (2l).** Colorless solid, mp 201–203 °C, lit. [26c] mp 204–205 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 8.06 (m, 1H, CH), 7.29 (d, <sup>3</sup>*J*(H,H) = 3.6 Hz, 1H, CH), 6.81–6.79 (m, 1H, CH); MS (neg-ESI): *m/z* (%): 135 (100) [M – H]<sup>–</sup>, 107 (20) [M – HN<sub>2</sub>]<sup>–</sup>, 79 (12) [M – HN<sub>4</sub>]<sup>–</sup>.

**5-(2'-Pyridyl)tetrazole (2m).** Colorless solid, mp 239–240 °C with decomp., lit. [26c] mp 239–240 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 9.24 (s, 1H, aromatic), 8.75–8.73 (m, 1H, aromatic), 8.44–8.41 (m, 1H, aromatic), 7.64–7.60 (m, 1H, aromatic); MS (neg-APCI): *m/z* (%): 146 (100) [M – H]<sup>–</sup>, 118 (44) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-Pyrazinetetrazole (2n).** Colorless solid, mp 197–199 °C, lit. [22a] mp 193–195 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 9.39 (s, 1H, aromatic), 8.88 (s, 2H, aromatic); MS (neg-ESI): *m/z* (%): 147 (100) [M – H]<sup>–</sup>, 119 (81) [M – HN<sub>2</sub>]<sup>–</sup>.

**5-(1,1-Diphenylethyl)tetrazole (2o).** Colorless solid, mp 144–146 °C, lit. [28b] mp 138–140 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 16.38 (br s, 1H, NH), 7.34–7.27 (m, 6H, aromatic), 7.10–7.08 (m, 4H, aromatic), 2.18 (s, 3H, CH<sub>3</sub>); MS (neg-ESI): *m/z* (%): 249 (100) [M – H]<sup>–</sup>.

**5-(2-(4'-Methyl)biphenyl)tetrazole (2p).** Brownish solid, mp 152–153 °C, lit. [22a] mp 150 °C; <sup>1</sup>H NMR (300 MHz, *d*<sub>6</sub>-DMSO, TMS)  $\delta$  = 16.30 (br s, 1H, NH), 7.70–7.63 (m, 2H, aromatic), 7.58–7.52 (m, 2H, aromatic), 7.12 (d, <sup>3</sup>*J*(H,H) = 7.8 Hz, 2H, aromatic), 6.98 (d, <sup>3</sup>*J*(H,H) = 7.8 Hz, 2H, aromatic), 2.29 (s, 3H, CH<sub>3</sub>); MS (neg-ESI): *m/z* (%): 235 (100) [M – H]<sup>–</sup>, 207 (9) [M – HN<sub>2</sub>]<sup>–</sup>.

**4.5. General Experimental Procedure for the Ring-opening Reaction of Oxazolines 3a–3i Under Microwave Conditions (Table 5).** Into a 5-mL microwave process vial equipped with a magnetic stir bar were introduced the respective oxazolines **3a–3i** (1.8 mmol), TMSN<sub>3</sub> (1.2 equiv, 284  $\mu$ L for the oxazolines **3a–3e** or 1.3 equiv, 308  $\mu$ L for the oxazolines **3f–3i**), and MeOH (300  $\mu$ L). TEA (0.1 equiv, 25.1  $\mu$ L) was added for the reactions with oxazolines **3h** and **3i**. The vials were sealed by capping with a Teflon septum fitted in an aluminum crimp top and the samples were irradiated in a Biotage Initiator 8 EXP 2.5 for the indicated time at the indicated temperature. After the reaction time had elapsed, the mixtures were cooled to 45 °C by compressed air. The solvent and any excess of reagent were removed under vacuum. This simple work-up provided GC-FID/H-NMR pure azides **4a** and **4b**. The remaining azides **4c–4i** were further purified by extraction with CHCl<sub>3</sub>/0.5 N HCl (20 mL/15 mL for the azides **4g** and **4h**, 20 mL/2  $\times$  15 mL for the other azides). The organic phases were dried over sodium sulfate and concentrated in vacuum to obtain the pure (GC-FID >99%) azide products (Table 5).

**4.6. General Experimental Procedure for the Ring Opening Reaction of Oxazolines 3a–3i Using the FlowSyn Reactor (Table 8).** The appropriate amounts of oxazolines **3a–3i** (and TEA (0.1 equiv) for the substrates **3h** and **3i**) were weighed into a volumetric flask (2 mL), and the flask was filled to the mark with MeOH (feed A). TMSN<sub>3</sub> was filled into a second flask (feed B). The streams A and B were mixed together at the indicated flow rates in a T-mixer at room temperature and the resulting stream was passed through the stainless-steel reactor coil (20 mL heated volume) heated at the indicated temperatures. The two streams were switched via a switching valve from pure solvent to reagent when the reactor was stable. Stream B was switched with a delay to ensure that both reagents arrive at the T-mixer at the same time. After passing the coil reactor, the mixtures were cooled in the plate HE to room temperature, and they left the reactor through a 34 bar BPR. For reactions at temperatures above 150 °C, a 52 bar BPR was applied. The

entire reaction mixtures were collected (plus 5 mL pre- and 10 mL post-collection) in a graduated cylinder and either the product mixtures were diluted for continuous flow hydrogenation (see Ref. [12]) or the azides **4a–4i** were isolated as described above.

**N-(2-Azidoethyl)acetamide (4a).** Colorless liquid,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 6.19 (bs, 1H, CONH), 3.46–3.38 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 2.00 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 170.71, 50.71, 38.92, 23.06; MS (pos-ESI):  $m/z$  (%): 129 (100)  $[\text{M} + \text{H}]^+$  [47].

**N-(2-Azidoethyl)propionamide (4b).** Colorless liquid,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 6.45 (bs, 1H, CONH), 3.39 (m, 4H,  $\text{CH}_2\text{CH}_2$ ), 2.20 (q,  $^3J(\text{H,H}) = 7.5$  Hz, 2H,  $\text{CH}_2$ ), 1.11 (t,  $^3J(\text{H,H}) = 7.5$  Hz, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 174.40, 50.72, 38.89, 29.46, 9.69; MS (pos-ESI):  $m/z$  (%): 143 (100)  $[\text{M} + \text{H}]^+$  [12].

**N-(2-Azidoethyl)benzamide (4c).** Colorless liquid,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 7.80–7.77 (m, 2H, ArH), 7.49–7.37 (m, 3H, ArH), 7.04 (bs, 1H, CONH), 3.62–3.56 (m, 2H,  $\text{CH}_2$ ), 3.52–3.48 (m, 2H,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 168.06, 134.09, 131.67, 128.56, 127.04, 50.73, 39.48; MS (pos-ESI):  $m/z$  (%): 191 (100)  $[\text{M} + \text{H}]^+$  [48].

**N-(2-Azido-1-phenylethyl)acetamide (4d).** Brownish oil,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 7.38–7.30 (m, 5H, ArH), 6.83 (d,  $^3J(\text{H,H}) = 7.8$  Hz, 1H, CONH), 5.19 (dt,  $^3J(\text{H,H}) = 8.1$ , 5.8 Hz, 1H, CONHCH), 3.60 (d,  $^3J(\text{H,H}) = 5.9$  Hz, 2H,  $\text{CH}_2\text{N}_3$ ), 2.00 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 170.30, 138.94, 128.84, 128.07, 126.76, 55.02, 52.89, 23.12; MS (pos-ESI):  $m/z$  (%): 205 (100)  $[\text{M} + \text{H}]^+$  [49].

**N-(1-Azido-3-phenylpropan-2-yl)acetamide (4e).** Yellow solid, mp 55–56 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 7.34–7.19 (m, 5H, ArH), 6.05 (d,  $^3J(\text{H,H}) = 7.9$  Hz, 1H, CONH), 4.33–4.29 (m, 1H, CONHCH), 3.46 (dd,  $J(\text{H,H}) = 12.3$ , 4.3 Hz, 1H,  $\text{CHHN}_3$ ), 3.32 (dd,  $J(\text{H,H}) = 12.4$ , 4.4 Hz, 1H,  $\text{CHHN}_3$ ), 2.91–2.78 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 1.97 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 169.97, 137.01, 129.18, 128.73, 126.86, 52.88, 50.04, 37.72, 23.29; MS (pos-ESI):  $m/z$  (%): 219 (100)  $[\text{M} + \text{H}]^+$  [12].

**N-((1R,2R)-1-Azido-3-methoxy-1-phenylpropan-2-yl)acetamide (4f).** White solid, mp 83–84 °C,  $[\alpha]_D^{30} = -125.9$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ),  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 7.42–7.31 (m, 5H, ArH), 5.81 (d,  $^3J(\text{H,H}) = 8.6$  Hz, 1H, CONH), 4.84 (d,  $^3J(\text{H,H}) = 7.5$  Hz, 1H,  $\text{CHN}_3$ ), 4.43–4.35 (m, 1H, CONHCH), 3.64 (dd,  $J(\text{H,H}) = 9.8$ , 4.4 Hz, 1H, CHH), 3.36 (s, 3H,  $\text{CH}_3$ ), 3.32 (dd,  $J(\text{H,H}) = 9.8$ , 3.8 Hz, 1H, CHH), 1.85 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 169.49, 136.28, 128.70, 128.55, 127.47, 70.38, 65.49, 59.05, 52.41, 23.15; MS (pos-ESI):  $m/z$  (%): 249 (100)  $[\text{M} + \text{H}]^+$  [12].

**N-(trans-2-Azidocyclohexyl)acetamide (4g).** Brownish solid, mp 80–82 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 5.84 (d,  $^3J(\text{H,H}) = 6.2$  Hz, 1H, CONH), 3.83–3.71 (m, 1H, CONHCH), 3.14 (td,  $^3J(\text{H,H}) = 10.6$ , 4.2 Hz, 1H,  $\text{CHN}_3$ ), 2.11–1.99 (m, 5H, includes  $\text{CH}_3$ ), 1.83–1.67 (m, 2H), 1.51–1.16 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 169.95, 63.86, 52.48, 32.09, 30.70, 24.25, 24.16, 23.49; MS (pos-ESI):  $m/z$  (%): 183 (100)  $[\text{M} + \text{H}]^+$  [12].

**N-(1-Azido-2-methylpropan-2-yl)acetamide (4h).** Yellow solid, mp 52–53 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 5.65 (s, 1H, CONH), 3.57 (s, 2H,  $\text{CH}_2$ ), 1.94 (s, 3H,  $\text{CH}_3\text{CO}$ ), 1.30 (s, 6H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 170.27, 57.30, 54.16, 25.17, 24.13; MS (pos-ESI):  $m/z$  (%): 157 (100)  $[\text{M} + \text{H}]^+$  [12].

**N-(1-Azido-2-methylpropan-2-yl)benzamide (4i).** Reddish solid, mp 86–87 °C,  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 7.73 (d,  $^3J(\text{H,H}) = 7.7$  Hz, 2H, ArH), 7.52–7.40 (m, 3H, ArH), 6.02 (s, 1H, CONH), 3.72 (s, 2H,  $\text{CH}_2$ ), 1.46 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  = 167.60, 135.24, 131.44, 128.58,

126.80, 57.71, 54.49, 25.28; MS (pos-ESI):  $m/z$  (%): 219 (100)  $[\text{M} + \text{H}]^+$  [12].

## 5. References and Notes

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32. Sulfiner<sup>®</sup> is a Siltek<sup>®</sup>-treated stainless-steel coil (i.e., chemical vapor-deposited multilayer silicon coating) that has the advantages of Teflon coatings or glass/fused silica coils without the problems associated with gas permeability and temperature limitations, associated with polymeric coatings such as Teflon, and with far higher flexibility and durability than glass/fused silica coils. The temperature limit of these coils is 600 °C. For further information, see www.restek.com
33. For the determination of the steady state yields, the post reaction stream was collected in a graduated cylinder.
34.  $\text{HN}_3$  dissolves some metals (M = Zn, Fe, Mn, and Cu) according to:  $\text{M} + 3 \text{HN}_3 + \text{H}^+ \rightarrow \text{M}(\text{N}_3)_2 + \text{N}_2 + \text{NH}_4^+$ ; see ref. 2b.
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