Microreactors

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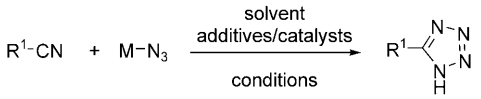
Synthesis of 5-Substituted 1*H*-Tetrazoles from Nitriles and Hydrazoic Acid by Using a Safe and Scalable High-Temperature Microreactor Approach**

Bernhard Gutmann, Jean-Paul Roduit, Dominique Roberge, and C. Oliver Kappe**

Dedicated to Professor K. Barry Sharpless

Interest in tetrazole chemistry over the past few years has been increasing rapidly, mainly as a result of the role played by this heterocyclic functionality in medicinal chemistry as a metabolically stable surrogate for carboxylic acid functionalities.[1] Additional important applications for tetrazoles are found in coordination chemistry, materials science, and as intermediates in a variety of synthetic transformations.[2]

The most common synthetic approach to prepare 5-substituted 1*H*-tetrazole derivatives involves the addition of azide salts to organic nitriles in a temperature range of typically 100–150 °C (Scheme 1).[1,2] A plethora of synthetic



a) M = H, b) M = Na, c) M = $Si(R^2)_3$, $Sn(R^2)_3$, $Al(R^2)_2$

Scheme 1. General azide–nitrile addition strategy to give tetrazole derivatives.

protocols and variations on this general theme have been reported in the literature during the past few years.[3–14] In the majority of cases, sodium azide (NaN_3) has been used as an inorganic azide source in combination with an ammonium halide as the additive employing *N*,*N*-dimethylformamide (DMF) or *N*-methylpyrrolidone (NMP) as dipolar aprotic solvents.[3,4] In some instances, the use of Brønsted[5] or Lewis acids,[6] heterogeneous[7] or nanocrystalline catalysts,[8] or stoichiometric amounts of Zn^{II} salts[9,10] have been reported as suitable additives to afford the desired azide–nitrile addition process. As an alternative to inorganic azide salts, trimethylsilyl,[11] trialkyl tin,[12] and organoaluminum azides[13] have been introduced as comparatively safe azide sources (sometimes prepared in situ), that have the added benefit of being soluble in organic solvents. Unfortunately, with very few exceptions, all of these methods require long reaction times (several hours to days) in combination with high reaction temperatures.

Based on atom economy and environmental impact, the conceptually most straightforward approach to the tetrazole nucleus involves the direct addition of hydrazoic acid (HN_3) to organic nitriles, first attempted in 1932.[15] Unfortunately, HN_3 is extremely toxic (comparable to HCN) and owing to the explosive nature and low boiling point (37 °C) of this high-energy material[16] procedures involving free HN_3 have not found any practical application in tetrazole synthesis so far.

In recent years, the use of microreactors and continuous flow technology in general has become increasingly popular in synthetic organic chemistry.[17,18] Enhanced heat- and mass-transfer characteristics and the ability to efficiently optimize reaction conditions by control of residence time add value to the technology. In addition, process intensification can readily be achieved by operating in a high-temperature/high-pressure regime.[19] A particularly attractive feature of microreaction technology is the ease with which reaction conditions can be scaled through the operation of multiple systems in parallel or other techniques, thereby readily achieving production scale capabilities.[20] Another key advantage of using microreactors compared to conventional batch reactors is the ability to safely process potentially hazardous compounds or reagents.[17,18] In a continuous flow system, synthetic intermediates can be generated and consumed in situ, which eliminates the need to store toxic, reactive, or explosive intermediates and thus makes the synthetic protocol safer.[17–21]

Herein, we describe a general and scalable method for the continuous flow synthesis of 5-substituted 1*H*-tetrazole derivatives via addition of HN_3 to organic nitriles. Key to this process is the in situ generation of HN_3 from NaN_3 and acetic acid in a microreactor coupled to an intensified high-temperature/high-pressure flow addition step to the nitrile. Under optimized conditions tetrazole compounds are formed with quantitative conversion in residence times of a few minutes, providing excellent purities and yields of isolated product.

An evaluation of existing protocols for batch tetrazole syntheses following the general azide–nitrile addition strategy (Scheme 1)[3–13] made the challenges of converting batch into flow conditions immediately apparent. Apart from the fact

[*] B. Gutmann, Prof. Dr. C. O. Kappe
Christian-Doppler-Labor für Mikrowellenchemie (CDLMC)
and, Institut für Chemie, Karl-Franzens-Universität
Heinrichstrasse 28, 8010 Graz (Austria)
Fax: (+43) 316-380-9840
E-mail: oliver.kappe@uni-graz.at
Homepage: http://www.maos.net
Dr. J.-P. Roduit, Dr. D. Roberge
Microreactor Technology, Lonza AG, 3930 Visp (Switzerland)
E-mail: dominique.roberge@lonza.com

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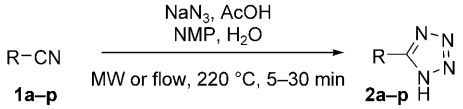
that most of the published procedures report reaction times of several hours (or even days) to obtain high conversions, in many instances the reaction mixtures were heterogeneous because of the presence of reagents, additives, or catalysts of low solubility in the chosen solvent system. In continuous flow/microreactor processing fully homogeneous reaction media are highly desirable. In addition, reaction times (=residence times) in flow should ideally be in the order of a few minutes for allowing a high throughput.

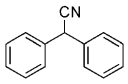
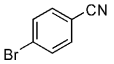
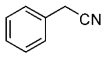
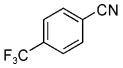
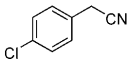
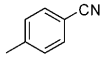
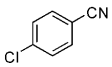
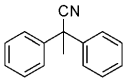
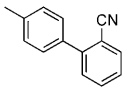
With this background an optimization campaign was started selecting 2,2-diphenylacetonitrile (**1a**) as a model compound for tetrazole formation (Table 1, MW). Based on atom economy and for economical reasons, NaN_3 was selected as an inexpensive azide source from the start. In a first set of experiments different solvents, Brønsted acids, and Lewis acids/additives were screened (see the Supporting Information for details). As it was clearly evident from the literature[3–13] that a high yielding and fast tetrazole synthesis would have to involve a high temperature regime, controlled sealed-vessel microwave heating was used initially as a process intensification method.[4] Optimization runs were generally performed on small scale (1 mmol of nitrile, 0.5–1.5 mL solvent) in a temperature range of 160–220 °C generating internal pressures up to 20 bar depending on the solvent system. 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 6×4 deep-well matrix in which pressure-resistant 5 mL Pyrex screw cap reaction vials were placed (Figure S1 in the Supporting Information).[22,23]

After analyzing the results from more than 200 independent experiments using 2,2-diphenylacetonitrile (**1a**) as a model compound, an optimum set of conditions that fulfilled both the requirement of reaction homogeneity and reaction speed, while at the same time providing clean and complete nitrile into tetrazole conversion involved the use of NMP as solvent, AcOH as Brønsted acid, and H_2O as cosolvent.[24] Applying two equivalents of NaN_3, a 7:2:1 ratio of NMP/AcOH/H_2O, and 220 °C as reaction temperature provided full conversion into the desired tetrazole **2a** at a 1 M nitrile concentration within 10 minutes and furnished a 85 % yield of isolated product (Table 1, MW).

To explore the scope and limitations of this new high-speed tetrazole synthesis a set of 16 aliphatic, aromatic, and heteroaromatic nitriles **1a**–**p** was subjected to the general reaction conditions, both using a single-mode microwave

Table 1: Batch and continuous flow synthesis of 5-substituted 1*H*-tetrazole derivatives.[a]



Substrate		Method	*t* [min][b]	Yield [%]	Work-up[c]	Substrate		Method	*t* [min][b]	Yield [%]	Work-up[c]
1a		MW	10	85	C	**1i**		MW	5	92	A
		flow[d]	15	82	C			flow	10	97	A
1b		MW	5	94	B	**1j**		MW	5	90/96	A/B
		flow	10	94	B			flow	10	97	A
1c		MW	5	90	B	**1k**		MW	5	92	A
		flow	10	92	B			flow	10	89	A
1d		MW	6	84/95	A/B	**1l**		MW	5	97	B
		flow	10	95	A			flow	10	98	B
1e		MW	5	94/98	A/B	**1m**		MW	5	77	D
		flow	10	98	A			flow	10	75	D
1f		MW	5	97	A	**1n**		MW	5	69	D
		flow	10	90	A			flow	10	68	D
1g		MW	5	98	A	**1o**		MW[e]	30	79	C
		flow	10	96	A			flow	–	–	–
1h		MW	6	80/88	A/B	**1p**		MW[e]	30	86	C
		flow	10	87	A			flow	–	–	–

[a] Conditions MW: 1.0 mmol of nitrile, 2.0 mmol of NaN_3, 1.0 mL of solvent (NMP/AcOH/H_2O = 7:2:1). Single-mode microwave heating at 220 °C (Biotage Initiator). Conditions flow: feed A (1 M solution of nitrile in NMP/AcOH = 5:2) at a flow rate of 0.69 mL min^{-1} and feed B (5.2 M NaN_3 in H_2O) at 0.31 mL min^{-1} at 220 °C (FlowSyn, Uniqsis Ltd, Figure 1).[25] [b] Reaction times refer to hold times at 220 °C in case of MW experiments (ramp time ca. 1.5 min, cooling time ca. 2.5 min), and residence times in the 10 mL heated coil for flow experiments. [c] Work-up methods: A: product precipitation 1 N HCl (pH 1); B: liquid-liquid extraction with $CHCl_3$ 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 $CHCl_3$ followed by pH adjustment with conc. HCl to pH 5. [d] 0.45 mL min^{-1} feed A and 0.21 mL min^{-1} feed B (residence time 15 min). [e] 4.0 equivalents of NaN_3, 1.5 mL of solvent. MW = microwave.

reactor and the conventionally heated SiC reaction block. For the microwave experiments, reaction times were further optimized, thus allowing even shorter addition times for most of the nitriles investigated. In fact, for 13 out of the 16 nitriles (Table 1, entries **1b–n**) 5–6 minutes at 220 °C were sufficient to reach full conversion. On the other hand, the sterically hindered nitriles **1o** and **1p** required four equivalents of NaN_3 and a 30 minute reaction time to reach completion. Despite the high reaction temperatures the azide-nitrile additions shown in Table 1 were remarkably clean, and for most cases no other products were observed in the crude reaction mixture (HPLC-UV at 215 nm). The yields of isolated products were generally very high (ca. 90 %), but somewhat dependent on the work-up strategy. In most instances, work-up simply involved precipitation with 1 N HCl and subsequent filtration of the product, although an extractive work-up generally provided somewhat higher yields owing to the water solubility of some tetrazole products (see Table 1 for details). Importantly, applying the SiC reactor plate and a 10 minute overall heating time on a standard hotplate, the 14 tetrazoles **2a–n** were synthesized in parallel in a single experiment, with conversion, product purities, and yields of isolated product being virtually identical to the microwave runs (Table S1 in the Supporting Information).

While the experiments described above provide a rapid means for reaction/diversity screening and optimization, the acidic conditions are clearly not suitable for a preparative large-scale batch synthesis of the desired target tetrazole derivatives. Owing to an excess of AcOH ($pK_a = 4.75$) as solvent in the reaction medium, considerable amounts of free HN_3 ($pK_a = 4.7$) will undoubtedly be present in both the liquid reaction mixture and the reactor headspace.[9] Explosive gas-phase mixtures of HN_3 in N_2 have been reported at concentrations as low as 8 %.[16] Of equal concern is the condensation of HN_3 on cold surfaces, the neat liquid being exceedingly sensitive to shock, with a decomposition enthalpy greater than that of trinitrotoluene.[16]

With these safety concerns in mind, we envisaged a continuous flow strategy for tetrazole synthesis; where HN_3 is generated in situ in a microreactor environment and subsequently consumed by addition to the nitrile (Figure 1). This

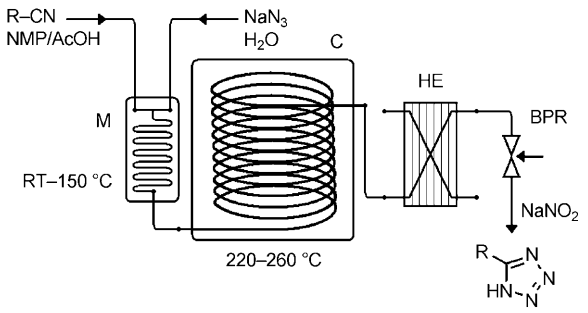


Figure 1. Schematic diagram for the continuous flow tetrazole synthesis performed in a FlowSyn reactor from Uniqsis Ltd.[25] M: static glass mixer block (2.0 mL internal volume); C: coil reactor (Sulfinert, 10.7 mL internal volume, 1.0 mm i.d.); HE: heat-exchanger; BPR: back pressure regulator (34 bar). For a graphic image of the used apparatus, see Figure S2 in the Supporting Information.

concept necessitates two independent feeds entering the microreactor system: an acidic solution of the nitrile in a NMP/AcOH mixture (feed A), and an aqueous NaN_3 solution (feed B). Following this idea, hazardous and toxic HN_3 will only be generated inside a suitable mixer (M) upon combination of the two streams. In a subsequent high-temperature coil reactor (C) the azide–nitrile addition occurs, before the reaction mixture is thermally quenched by a heat-exchanger (HE) and exits the continuous flow system through a back-pressure regulator followed by an immediate chemical quench to destroy any unreacted HN_3. Because the continuous flow system is run liquid-filled without vapor-phase headspace and dilute solutions of HN_3 (< 20 % by weight) are regarded as stable, the risk of an HN_3 explosion is significantly reduced.[16]

Owing to the limited solubility of NaN_3 in H_2O (417 mg mL^{-1} at 17 °C) an adjustment of the NMP/AcOH/H_2O solvent mixture composition to 5:2:3 was required in order to implement the two feed concept.[24] Appropriate feed compositions for the anticipated flow transformation involved a ca. 1.0 M solution of the corresponding nitriles **1a–n** in a 5:2 NMP/AcOH mixture (feed A), and a 5.2 M solution of NaN_3 in H_2O (feed B). Importantly, this corresponds to approximately 2.5 equivalents of NaN_3 and thus a maximum initial concentration of HN_3 in these protocols of approximately 1.6 M (ca. 7 % by weight), which is far below the published safety limit of 20 %.[16] To ensure that the reaction system remains homogeneous and to evaluate if under these modified conditions high conversions/purities could still be obtained, batch microwave runs were initially performed. Gratifyingly, increasing the reaction time to 10 minutes (15 min for nitrile **1a**) at 220 °C (18 bar) full conversion and high yields of isolated product were also furnished under these less concentrated (ca. 0.69 M in nitrile) conditions utilizing a mixture of 1 mL of feed A and 0.45 mL of feed B (Table S2 in the Supporting Information). For nitriles **1g**, **1i**, and **1k** precipitation of starting material was observed upon addition of aqueous feed B at room temperature, thus indicating the necessity of a heated mixing step in the continuous flow experiment (Figure 1). An additional concern was the choice of reactor coil material for the high-temperature azide–nitrile addition. As HN_3 cannot be used in combination with heavy metals because of safety concerns,[16] a passivated silica-coated stainless-steel coil (Sulfinert) of 10.7 mL internal volume (i.d. 1.0 mm) was employed, mimicking a glass environment.[26]

For flow processing (Figure 1), feed A containing the nitrile was pumped into the mixer (M) at a flow rate of 0.69 mL min^{-1} and feed B (NaN_3) at 0.31 mL min^{-1} (providing a ca. 2.5 molar excess of azide). Mixing was either performed in a T-piece at room temperature or in a glass static mixer block at 150 °C (for nitriles **1g**, **1i**, and **1k**). The resulting stream was passed through the Sulfinert reactor coil (ca. 10 mL heated volume, C) at 220 °C at a system pressure of 36 bar. At the overall flow rate of 1.0 mL min^{-1} this corresponds to a residence time of around 10 minutes in the reactor coil mimicking the batch optimization runs performed under microwave conditions (Table S2 in the Supporting Information). After passing through the heat exchanger (HE)

providing a rapid thermal quench to 25 °C, and through the back pressure regulator (BPR), the reaction mixture was flowed directly into a reservoir of aqueous $NaNO_2$ to decompose any unreacted HN_3.[27,28] Gratifyingly, using the high-temperature/high-pressure continuous flow processing regime complete conversion and virtually identical yields for tetrazole products **2a**–**n** were obtained compared to the MW batch experiments (Table 1, flow), the only exception being tetrazoles **1o** and **1p** which, because of the extended reaction times required for their preparation and low solubility, were not synthesized in flow. In an attempt to further intensify this process and to increase throughput, the addition of HN_3 to benzonitrile (**1d**) was also executed at 260 °C, thus allowing a reduction of the residence time to only 2.5 minutes. Under these conditions, applying a flow rate of 4.0 mL min^{-1} 240 mL of reaction mixture could be processed through the continuous flow setup within one hour allowing the isolation of 18.9 g (89 %) tetrazole product in similar high purity compared to the 220 °C run.

In conclusion, we have demonstrated that 5-substituted 1*H*-tetrazole derivatives can be synthesized in unprecedented efficiency using a high-temperature/high-pressure microreactor approach. Key to the success of this protocol is the in situ generation of toxic and explosive HN_3 within the microreactor environment and the use of extreme temperatures as process intensification tool. The catalyst-free method uses inexpensive NaN_3, benign solvents, and does not require any other additives. Based on atom economy, environmental impact, and cost the laboratory scale synthesis described here appears to be well suited for a safe industrial scale preparation of tetrazole compounds. The generation and secure handling of extremely hazardous HN_3 itself in a microreactor environment as described here may in fact allow other synthetic chemistry using this high-energy reagent to be performed in the future.

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[26] Sulfinert is a Siltek-treated stainless-steel coil (i.e. chemical vapor deposited multilayer silica coating) that has the advantages of Teflon coatings or glass/fused silica coils without the problems with gas permeability and temperature limitations associated with polymeric coatings such as Teflon coatings, 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.

[27] On an industrial scale, this chemical quench step ($HN_3 + HNO_2 \rightarrow N_2O + N_2 + H_2O$, Ref. [16b]) could be performed in-line in flow as the reaction mixture remains homogeneous upon addition of aqueous $NaNO_2$.

[28] It should be noted that owing to the absence of a reactor headspace in the continuous flow environment, the available concentration of HN_3 should in fact be significantly higher than in a sealed vessel microwave batch environment, where a large amount of this volatile reagent can be expected to be in the gas phase. For similar observations made with volatile amines in microreactors, see: M. W. Bedore, N. Zaborenko, K. F. Jensen, T. F. Jamison, *Org. Process Res. Dev.* **2010**, *14*, 432.

