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in a Continuous Flow Microreactor*

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Citation: Palde, Prakash B., and Timothy F. Jamison. "Safe and Efficient Tetrazole Synthesis in a Continuous-Flow Microreactor." *Angewandte Chemie International Edition* 50.15 (2011): 3525–3528.

As Published: <http://dx.doi.org/10.1002/anie.201006272>

Publisher: Wiley Blackwell

Persistent URL: <http://hdl.handle.net/1721.1/76267>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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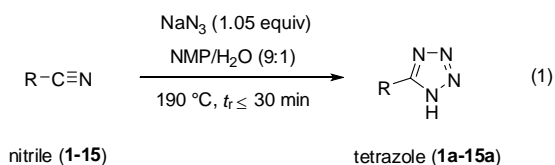


Safe and Efficient Tetrazole Synthesis in a Continuous Flow Microreactor**

Prakash B. Palde and Timothy F. Jamison*

Tetrazoles are an important class of heterocycles in a wide range of applications, such as, organocatalysis and transition metal catalysis, propellants, explosives, and perhaps most commonly, as non-classical isosteres of carboxylic acids in medicinal chemistry.^[1,2] This broad utility has prompted significant effort toward tetrazole synthesis,^[3] and notable among these is that of Sharpless, in which aqueous zinc bromide (ZnBr₂) facilitates the assembly of tetrazoles from nitriles and sodium azide (NaN₃).^[3e] Nevertheless, the majority of reported methods are generally not suited for large scale synthesis; they require explosive and/or expensive reagents, toxic metal-containing compounds, or excess azide. The most significant hazard is the generation of hydrazoic acid (HN₃), particularly in reactions conducted in the presence of even trace amounts of Brønsted acids.^[4]

Continuous flow synthesis is emerging as a powerful technology complementary in several contexts to batch synthesis in flasks or vessel reactors.^[5] As only small quantities of reagents and products are exposed to the reaction conditions at a given time, the risks associated with hazardous materials are minimized, and transformations using them are thus rendered much safer. Flow would thus appear to be an appropriate reaction format for the synthesis of tetrazoles from nitriles and an azide source. During the preparation of this manuscript a collaborative effort between Kappe and Lonza reported an exquisitely engineered system for the continuous flow synthesis of tetrazoles using HN₃.^[6] Generated in situ from NaN₃ and acetic acid, HN₃ (approx. 2.5 equiv at 1.6 M) may be used at elevated temperatures and pressures to prepare a range of tetrazoles from the corresponding nitriles.



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[**] We are grateful to the Novartis-MIT Center for Continuous Manufacturing for financial support and to several colleagues at MIT (Stephen L. Buchwald, Klavs F. Jensen, and their coworkers) and Novartis (Gerhard Penn, Berthold Schenkel, Oljan Repic, Thierry Schlama, Mike Girgis, Lukas Padeste, and Felix Kollmer) for insightful discussions.



Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

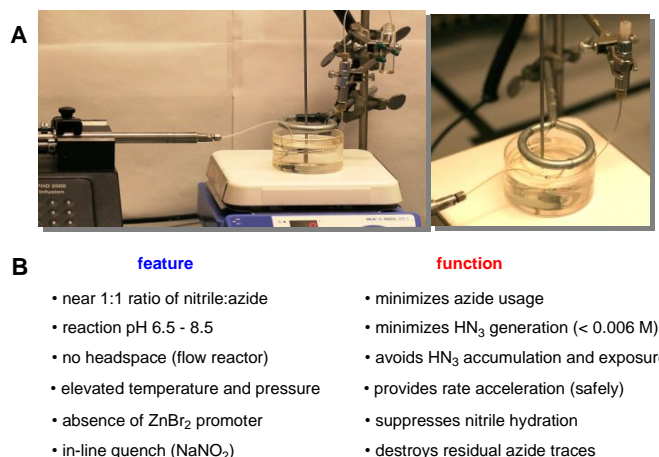


Figure 1. (A) Photographs of flow reactor for tetrazole synthesis. See Supporting Information for parts list and instructions for assembly and operation (video). (B) Summary of the function of each reactor feature.

From the outset of our investigations, described herein, we took a conceptually and technically different approach, establishing the following as fundamental requirements of our method: avoid the use and generation of HN₃,^[7] require only a slight excess of azide (in any form), develop a system that can be assembled easily such that it may be implemented both in the laboratory (education and research) and, with straightforward modification, on manufacturing scale. In addition to being safer (no HN₃, minimal azide usage), easily assembled (see Figure 1 and video provided in Supporting Information) and less expensive (syringes, syringe pumps, oil bath, standard tubing and fittings), this method is, perhaps unexpectedly, faster and higher yielding in many cases. Other features include the fact that neither a metal catalyst nor promoter is required and the inclusion of a simple in-line, post-reaction treatment with NaNO₂ to quench the vanishingly small traces of remaining azide.

We began our investigations by evaluating several reported methods of tetrazole synthesis with the aim of finding one that would be amenable to the requirements listed above. In early stages, small-scale microwave reactions provided a useful and informative bridging basis of comparison between batch and flow^[8] (Table S1, Supporting Information). Nitrile **1** (eq 1, R = *p*-anisyl) was chosen as the starting point as it is of moderate reactivity in most tetrazole syntheses, largely due to the electron-donating effect of the methoxy group.^[9] The conditions reported by Sharpless^[3e] and later shown to be effective under microwave irradiation by Fang^[3b] (Table S1, entries 4-6) showed the greatest promise for development of a flow process. With nitrile **1** a reaction temperature of 140 °C provided the highest yield of desired tetrazole **1a** (65%) in 30 min. The solution mixture remained homogenous throughout the entire course of the reaction, but an undesired byproduct, carboxamide **1b** (see Supporting Information), resulting from nitrile hydration was also obtained in significant quantities (9% yield).^[10]

Nevertheless, this lead result served as the starting point for the development of a straightforward flow process (Figure 1 and Table 1). Nitrile **1**, NaN₃, and ZnBr₂ in a clear, homogeneous organic/aqueous solution were pumped into a simplified microreactor assembly consisting of PFA tubing immersed in an oil bath and equipped with a 250 psi backpressure regulator at the distal end. The lack of reactor headspace provided an immediate advantage over the batch microwave conditions: Much higher temperatures were possible, with no increased risk of explosion or exposure, thus providing significant acceleration of the desired transformation in a safe manner. We observed a considerable dependence of conversion on solvent selection, and a 9:1 mixture of NMP:water provided the best balance of rate and yield, while maintaining reaction homogeneity throughout (entries 2-4).

This observation and a few other modifications achieved one of the critical requirements that we had established for the process, namely, minimal use of azide (1.05 equiv relative to nitrile **1**). Moreover, as long as the solvent mixture was largely organic, the amount of NaN₃ and ZnBr₂ could be decreased to 1.05 and 0.50 equivalents, respectively, with no reduction in conversion or yield (entries 5-6). Doubling the substrate concentration did increase conversion, but nitrile hydration to carboxamide **1b** reappeared as a significant competing process. However, omission of the ZnBr₂ suppressed this undesired pathway to below the limit of detection (HPLC, approx 1%) with only a minimal decrease in conversion of desired tetrazole **1a** (entries 7-8). Nitrile hydration is thus dependent upon ZnBr₂, whereas tetrazole formation is only minimally so.^[3e, 11]

Table 1. Optimization of continuous flow tetrazole synthesis^[a]

Entry	Solvent	NaN ₃ (equiv)	ZnBr ₂ (equiv)	Conv. (%) ^[b]	yield (%) ^[b]	
					1a	1b
1 ^[c]	THF:H ₂ O (1:4)	4	2	90	76	10
2	IPA:H ₂ O (1:4)	4	2	79	64	11
3	NMP:H ₂ O (1:4)	4	2	95	83	8
4	NMP:H ₂ O (1:4)	2	1	81	72	7
5	NMP:H ₂ O (1:4)	1.05	0.5	61	56	4
6	NMP:H ₂ O (9:1)	1.05	0.5	63	61	< 1
7 ^[d]	NMP:H ₂ O (9:1)	1.05	0.5	86	78	7
8 ^[d]	NMP:H ₂ O (9:1)	1.05	0	83	81	< 1

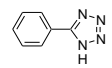
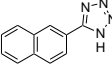
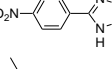
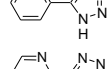
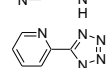
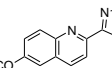
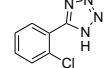
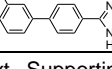
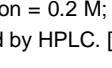
[a] See Supporting Information and eq 1. Unless otherwise noted, substrate concentration [1]₀ = 0.2 M; reaction temperature = 190 °C; residence time (t_r) = 20 min. [b] Determined by HPLC. [c] Reaction temperature = 170 °C. [d] [1]₀ = 0.4 M; t_r = 30 min.

Many nitriles underwent complete conversion to the corresponding tetrazoles under these optimized conditions (Table 2). Nitriles **2** and **3**, bearing no ostensible electron-donating or withdrawing groups on the aromatic ring, were transformed to tetrazoles **2a** and **3a** in near-quantitative yield in 20 min. The electron-poor nitrile **4** behaved similarly, as did *m*-tolunitrile (**5**) and heteroaromatic nitriles **6-8**. Slightly reduced conversions were observed in case of sterically-hindered nitrile **9** and biphenyl-substituted nitrile **10**.

The success with nitrile **1** prompted us to test the reactivity of other electron-rich nitriles under these conditions. Moderate conversion, yet excellent yield based thereon, was observed for electron-rich nitriles **11** and **13** (Table 3). As observed with the nitrile **1**, **11-17** showed higher conversion at substrate concentration = 0.4 M. Biphenyl nitriles **14-15** displayed both good conversion and good yield. Notably, chiral nitrile **15** provided **15a**, a derivative of which (no CBZ group) has found utility as an organocatalyst,^[1b] in > 99% ee and 92% yield based on conversion. The electron rich as well as sterically hindered nitrile **12a** showed poor conversion and yield under these conditions. Most importantly, however, no

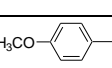
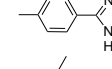
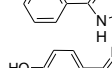
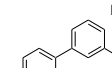
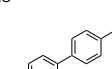
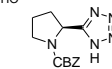
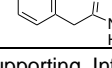
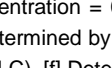
carboxamide was observed in *any case* in the absence of ZnBr₂, even at extended residence times, and a ten-fold scale-up (10× longer tubing (same diameter), 10× faster flow rate) using these conditions proceeded as expected, affording 3.5 g of **3a** in 12 h.

Table 2. Scope of continuous flow tetrazole synthesis^[a]

tetrazole product	conversion (%) ^[b]	yield (%) ^[b]
2a 	100	98 (96) ^[c]
3a 	99	95 (94) ^[c]
4a 	98	95 (93) ^[c]
5a 	90	85 (81) ^[c]
6a 	94	93 (90) ^[c]
7a 	100	96 (94) ^[c]
8a 	99	98 (97) ^[c]
9a 	80	77 (75) ^[c]
10a 	81	79

[a] See text, Supporting Information, and eq 1. In all cases, nitrile concentration = 0.2 M; reaction temperature = 190 °C; t_r = 20 min. [b] Determined by HPLC. [c] Isolated yield.

Table 3. Effects of concentration and residence time^[a]

tetrazole product	conversion (%) ^[b]	yield (%) ^[b]
1a 	83 ^[d]	81 (79) ^[c]
11a 	61	57 (51) ^[c]
12a 	25	25 (23) ^[c]
13a 	49 ^[d]	48 (45) ^[c]
14a 	86	84 (81) ^[c]
15a 	82	77
16a 	71 ^[e]	65
17a 	51 ^[f]	50 ^[f] (48) ^[c]

[a] See Supporting Information and eq 1. Unless otherwise noted nitrile concentration = 0.4 M; reaction temperature = 190 °C; t_r = 20 min. [b] Determined by HPLC. [c] Isolated yield. [d] t_r = 30 min. [e] ee > 99% (HPLC). [f] Determined by ¹H NMR.

To demonstrate the scale-up capabilities of our process beyond laboratory scale, we carried out the synthesis of **3a** on Uniqsis FlowSyn continuous flow reactor. FlowSyn is an integrated continuous flow reactor system that uses a pair of high pressure pumps to deliver reagent solutions through a T-mixer into the electrically heated flow coil or column reactors.^[12] The homogenous solution of reagents ([**3**] = 1M; [NaN₃] = 1.05 M) in NMP:H₂O (7:3) was pumped using a single pump through a coiled PFA tubing reactor (volume of heated zone ~ 6.9 mL) with a flow rate of 0.35 mL/min (*t_r* = 20 min) at 190 °C (see Supporting Information). The flow process was run continuously for 2.5 h to obtain 9.7 g of **3a** in 96 % yield. This corresponds to a product output of 4.85 g/h or 116 g/day for the tetrazole **3a**.

Overall, this flow synthesis of 5-substituted tetrazoles is safe, practical, efficient, and straightforward. It enjoys a broad scope, and in all cases the yield based on conversion is greater than 90%, in many cases nearly quantitative. The hazards associated with HN₃ are essentially eliminated, shock-sensitive metal azides such as Zn(N₃)₂ are eschewed, and any residual NaN₃ is quenched in-line with NaNO₂. Given these features and the widespread applications of tetrazoles, this method may find use on any scale, from laboratory to manufacturing.

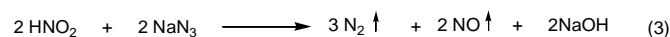
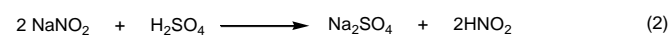
Finally, it should be emphasized that the most important attributes of this process (high yield, near-equimolar nitrile:azide ratio, no ZnBr₂-promoted nitrile hydration, minimal HN₃ generation, and short reaction time) are collectively possible *only* because the reactions can be conducted at elevated temperature (190 °C). This critical reaction variable is in turn feasible *only* because the reaction format is flow, wherein there is no headspace in which HN₃ could accumulate to an explosive level. That there is no headspace therefore not only obviates several hazards, but also improves the method. A closed-system batch process at 190 °C (microwave or otherwise) would be far too hazardous, and without elevation of the reaction temperature, the reaction rate would be well below a usable level. It is thus demonstrated in this case that flow not only is far safer than batch, but also is the necessary and enabling technology for this process.

Experimental Section

General protocol for continuous-flow synthesis of 5-substituted tetrazoles: NaN₃ (138 mg, 2.1 mmol, 1.05 equiv.) was dissolved in 0.5 mL of water and this solution was added to the nitrile substrate (2 mmol, 1 equiv.) dissolved in 4.5 mL of NMP. The resulting solution was filled in a 10 mL stainless steel syringe (Harvard Apparatus, high pressure stainless steel syringe with 1/16 inch SWAGelok®), which was then charged to a syringe pump (Harvard PHD 2000). The syringe was connected to the assembled tubular coiled reactor (please see the supporting info video for the dimensions as well as stepwise assembly of the tubular reactor). The coiled-portion of the tubular reactor (constituting a volume of 120 μL) was dipped in an oil bath (heating source) and a 250 psi back pressure regulator (Upchurch® Scientific) was installed at the distal end of this tubing followed by the outlet tubing. For substrates like *o*-tolunitrile (**11**) where significant amount of unreacted NaN₃ is left after the reaction, streams of NaNO₂ (20 % in H₂O) and H₂SO₄ (20 % in H₂O) were introduced in the post-reaction stream in order to quench the excess azide (eq 2 and 3). The reaction mixture was pumped through the tubular reactor at a rate of 6 μL/min, and the temperature of the oil bath was set to 190 °C. This resulted in a 20 min residence time (*t_r*) for reaction mixture in the part of tubing immersed in the oil bath. *This flow process was carried out behind an explosion shield for personal safety.* After the reactor reached a steady state (flowing 2-3 full reactor volumes), the post-reaction stream was collected in a clean vial for 5-6 h. To determine the isolated yield, 2 mL of the post-reaction stream was diluted with 40 mL of water. The solution was

acidified to pH 1 (except for the heterocyclic substrates **6**, **7** and **8**) using 3 N HCl solution and stirred vigorously for 30 min. A white precipitate appeared which was extracted into non-aqueous layer using 20 mL of ethyl acetate. The organic layer was washed with 3 N HCl (2 x 10 mL) and concentrated to yield the crude product. This crude product was taken in 10 mL of 0.25 N NaOH solution and stirred vigorously for 20 min. The solution was then washed with ethyl acetate (10 mL x 2) and acidified to pH 1 using 3 N HCl. The tetrazole product precipitated (in most but not all cases) upon stirring. This acidified solution or suspension was again extracted into 20 mL ethyl acetate and the organic layer was separated. The aqueous layer was washed with ethyl acetate (20 mL x 2). The organic layers were combined, concentrated and dried under vacuum to yield pure product.

To determine isolated yield for heterocyclic substrates **6**, **7** and **8**, the reaction was diluted with water and the pH was adjusted to 6.5 with vigorous stirring. The resulting precipitate was extracted into 20 mL ethyl acetate and the organic layer was separated. The aqueous layer was washed with ethyl acetate (20 mL x 2). The organic layers were combined, concentrated and dried under vacuum to yield pure product.



Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

Keywords: tetrazoles · microreactors · azides · synthetic methods

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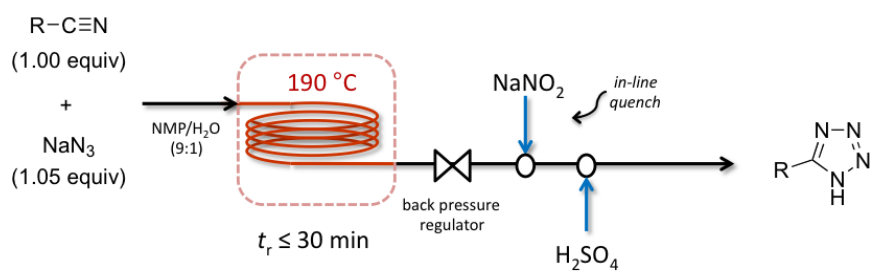
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- [11] For detailed comparisons of the effects of ZnBr₂ (presence vs. absence) in this transformations, please see the Supporting Information.
- [12] <http://www.uniqsis.com>
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Layout 2:

Microreactors

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Safe and Efficient Tetrazole Synthesis in a Continuous Flow Microreactor



The synthesis of 5-substituted tetrazoles in flow is safe, practical, efficient, and straightforward. It requires no metal promoter and uses a near-equimolar amount of NaN₃, yet nonetheless displays a broad substrate scope. In all cases the yield based on conversion is greater than 90%, in many cases nearly quantitative. The hazards associated with HN₃ are essentially eliminated, shock-sensitive metal azides such as Zn(N₃)₂ are avoided, and any residual NaN₃ is quenched in-line with NaNO₂. This method thus provides convenient and safe tetrazole synthesis on any scale, from laboratory to manufacturing.