Articles

Preparation of 5-Substituted 1*H*-Tetrazoles from Nitriles in Water†

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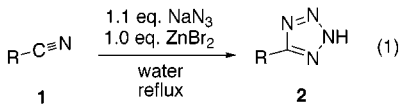
The addition of sodium azide to nitriles to give 1*H*-tetrazoles is shown to proceed readily in water with zinc salts as catalysts. The scope of the reaction is quite broad; a variety of aromatic nitriles, activated and unactivated alkyl nitriles, substituted vinyl nitriles, thiocyanates, and cyanamides have all been shown to be viable substrates for this reaction.

The literature on tetrazoles is expanding rapidly.[1] This functional group has roles in coordination chemistry as a ligand, in medicinal chemistry as a metabolically stable surrogate for a carboxylic acid group,[2] and in various materials science applications, including specialty explosives.[3] Less appreciated, but of enormous potential, are the many useful transformations that make tetrazoles versatile intermediates en route to substituted tetrazoles, and especially to other 5-ring heterocycles via the Huisgen rearrangement.[4] The prime reason for the scarcity of practical applications for these sophisticated tetrazole-based reactions is the lack of appealing synthetic routes to the key intermediates, RCN_4H (**2**). We report here a safer and exceptionally efficient process for transforming nitriles into tetrazoles in water; the only other reagents are sodium azide and a zinc salt (eq 1).



(1)

The most convenient route to 5-substituted 1*H*-tetrazoles (**2**) is the addition of azide ion to nitriles (**1**).[5] The literature is replete with methods to perform this transformation; they fall into three main categories: those that make use of tin or silicon azides,[6] those that use strong Lewis acids,[7] and those that are run in acidic media.[8] Each of these has one or more of the following drawbacks: expensive and toxic metals, severe water sensitivity, and the presence of hydrazoic acid, which is highly toxic and explosive as well as volatile. The few methods that seek to avoid hydrazoic acid liberation during the reaction, by avoiding acidic conditions, require a very large excess of sodium azide.[9] In addition, all of the known methods use organic solvents, in particular, dipolar aprotic solvents such as DMF. This is one of the solvent classes that process chemists would rather not use.[10] We sought to find a method that avoided these drawbacks and was easy to use on both a laboratory and industrial scale.

Water is rarely used or even considered as a solvent for organic reactions. The two foremost reasons why chemists shy away from water is the lack of solubility of most organic compounds in this medium and/or concerns that the high "acid/base" reactivity will interfere with the desired reaction.

However, it is hard to ignore water as a solvent. Beyond being environmentally benign, its extraordinary physical properties are widely appreciated.[11] While the

† Dedicated to Professor Harry H. Wasserman on the occasion of his 80th birthday.

‡ Recipient of the 2001 Nobel Prize in Chemistry.

(1) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 4.

(2) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151−183.

(3) (a) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467−526. (b) Hiskey, M.; Chavez, D. E.; Naud, D. L.; Son, S. F.; Berghout, H. L.; Bome, C. A. *Proc. Int. Pyrotech. Semin* **2000**, *27*, 3−14.

(4) Moderhack, D. *J. Prakt. Chem.* **1988** *340*, 687−709.

(5) Wittenberger, S. J. *Org. Prep. Proced. Intl.* **1994**, *26*(5), 499−531.

(6) (a) Dunica, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395. (b) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139−4141. (c) Curran, D. P.; Hadida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997−9006.

(7) (a) Wiberg, V. E.; Michaud, H. *Z. Naturforsch., Teil B* **1954**, *9*, 497. (b) Grzonka, Z.; Liberek, B. *Roczniki Chemii* **1971**, *45*, 967−980. (c) Huff, B. E.; Staszak, M. A. *Tetrahedron Lett.* **1993**, *34*, 8011−8014. (d) Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 1(13), 4462−4465.

(8) (a) Mihina, J. S.; Herbst, R. M. *J. Org. Chem.* **1950**, *15*, 1082−1092. (b) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908−3911. (c) Ostrovskii, V. A.; Poplavskii, V. S.; Koldobskii, G. I.; Erusalinkii, G. B. *Khim. Geterotsikl. Soedin.* **1992**, 1214−1217. (d) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910−914.

(9) For examples, see: (a) Sauer, J.; Huisgen, R.; Strum, H. J. *Tetrahedron* **1960**, *11*, 241−251. (b) Gallante, R. J. U.S. Patent 5,502,191, 1995. (c) Tokuhara, G.; Yamaguchi, T.; Iwasaki, T. WO Patent 1996−37481, 1996. A good method for the amelioration of the excess azide/hydrazoic acid with sodium nitrite was first reported in Reith, J. F.; Bowman, J. H. A. *Pharm. Weekbl.* **1930**, *67*, 600. A good review can be found in: Federoff, B. T., Ed. *Encyclopedia of Explosives and Related Items*; Picatinny Arsenal: Dover, NJ, 1960; Vol. 1, p A574.

(10) Anderson, N. *Practical Process Research & Development*; Academic Press: San Diego, CA, 2000; Chapter 4.

(11) (a) Reichardt, C. *Solvents and Sovent Effects in Organic Chemistry*; VCH Verlagsgesellschaft mbH: Weinheim, Germany 1988. (b) Brack, A *Adv. Space Res.* **1999**, *24*(4), 417−433.

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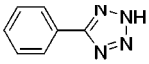
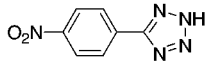
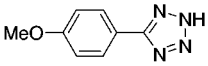
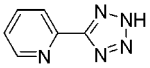
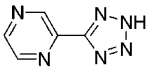
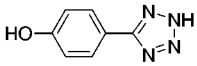
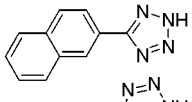
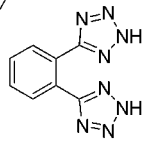
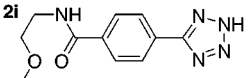
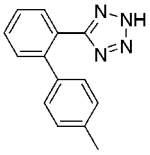
traditional concerns (vide supra) seem well founded, there are many examples demonstrating that reactions commonly performed using organic solvents work equally well, if not better, in water. Over the past few years, we have encountered numerous examples of water as the "perfect" solvent: e.g., in (1) osmium-catalyzed dihydroxylation and aminohydroxylation,[12] (2) nucleophilic opening of epoxides and aziridines,[13] (3) cycloaddition reactions of all kinds,[13] (4) most oxime ether, hydrazone, and aromatic heterocycle condensation processes,[14] and (5) the formation of an amide from a primary amine and an acid chloride using aqueous Schotten−Baumann conditions.[15] In many of these cases, either the starting material, product, or both are relatively insoluble in water; in others, the reagents are of a water-sensitive nature, yet the reactions proceed with high yield and fewer side products than when organic solvents are used. Thus encouraged, we envision a special style of organic synthesis, one based on an entire family of reactions for which water is the best "solvent".

As a result of these endeavors, we have found that in the presence of zinc salts[9b,c] tetrazole formation proceeds with excellent yields and scope in refluxing water.[16] Thanks to the low pK_a of 1*H*-tetrazoles (ca. 3−5) and their highly crystalline nature, a simple acidification is usually sufficient to provide the pure tetrazoles.

Another goal was to create a procedure that avoids the release of hydrazoic acid. An aqueous solution of 1 M zinc bromide has ca. pH 7, and when sodium azide is added (1 M), it is slightly alkaline, ca. pH 8; consequently, even at 100 °C, release of hydrazoic acid is minimized. Still, as the pK_a of hydrazoic acid is 4.7, one might expect a small amount of hydrazoic acid to be liberated during the reaction at the temperatures and concentrations involved. Indeed, when the reactions were run at a concentration of 1 M in sodium azide and 1 M in $ZnBr_2$, we were able to detect a small amount of liberated hydrazoic acid in the headspace above the refluxing solvent;[17] when the concentration was dropped to 0.5 M, no hydrazoic acid could be detected. On the contrary, in the headspace above a solution of 0.5 M sodium azide and 0.5 M ammonium chloride in dimethyl formamide at 100 °C, hydrazoic acid was clearly present in much higher concentrations and even more so at 125 °C, the conditions used in the most common procedure for making tetrazoles.[8b] By only using 1.05 equiv of sodium azide, the risk of hydrazoic acid liberation upon workup is minimal. However, in some cases such as benzonitrile (**1a**), the yields were lower; compare a 76% yield of 5-phenyltetrazole when 1.05 equiv of sodium azide is used with a 93% yield when 1.50 equiv is used.

Table 1. Aromatic Tetrazoles

Entry	Tetrazole[a]	temp. time	Yield	m.p.
2a		reflux 24hr	76%	215-216°C
2b		reflux 24hr	94%	220°C
2c		reflux 48hr	86%	231-232°C
2d		reflux 6hr	79%	211°C
2e		reflux 2hr	83%	193-195°C
2f		140°C 24hr	96%	234-236°C
2g		140°C 48hr	73%	205-207°C
2h		reflux 48hr	64%	228-230°C
2i		reflux 12hr	67%	158-160°C
2j		170°C 48hr	67%	150°C

[a] These reactions were run on 20 mmol scale.

A wide variety of nitriles were converted to tetrazoles on a 20 mmol scale. Other things being equal, the more electron-poor a nitrile, the faster it reacts. Aromatic nitriles (see Table 1) with a variety of substituents (**1a**,**b**,**c**,**i**) reach completion within several days at reflux. Electron-poor aromatic and heteroaromatic nitriles, such as 2-cyanopyridine and cyanopyrazine (**1d**,**e**), are complete within a few hours. Some electron-rich aromatic nitriles (**1f**,**g**) require higher temperatures, which are achieved using a sealed glass pressure reactor. Ortho-substituted aromatic nitriles are the most challenging, sometimes proceeding at reflux **(1h)**, but often requiring much higher temperatures (**1j**). We have not been able to achieve significant conversion of any aromatic nitriles bearing an sp^3-hybridized substituent in the ortho position.[18]

Unactivated alkyl nitriles (see Table 2) also require very high temperatures (**1k**,**l**), but with electron-with-

(12) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*(8), 2483−2547. (b) Wang, Z. M.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*(26), 8302−8303. (c) Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2001**, *40*(18), 3455−3457.

(13) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2001**, *40*(11), 2004−2021.

(14) (a) Patai, S., Ed. *The Chemistry of the Carbon−Nitrogen Double Bond*; Interscience Publishers: London, U.K., 1070. (b) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison-Wesley Longman Ltd: Harlow, U.K., 1997.

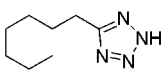
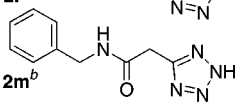
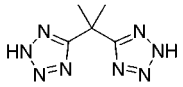
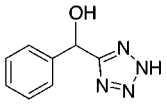
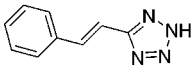
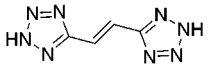
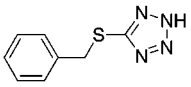
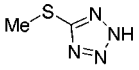
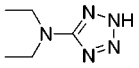
(15) Sonntag, N. O. V. *Chem. Rev*. **1953**, *52*, 237−416.

(16) Note that the high heat capacity of water when used as a solvent strongly mitigates the explosion hazards from endergonic groups such as aromatic azides and nitro compounds. In the present system, it is important that an aqueous sodium azide solution is very stable at reflux. For example, this system has been used, under $R_4N^+X^-$ catalysis, to displace two chlorides from neat 3,3-bis(choromethyl)-oxetane so that the organic phase becomes pure 3,3-bis(azidomethyl)-oxetane plus a few percent water. This is run on a several hundred kilogram scale, and the crude material is directly transferred to 55 gallon drums for shipment. See: Malik, A. A.; Manser, G. E.; Carson, R. P.; Archibald, T. G. U. S. Patent US 5,523,424, 1996.

(17) A strip of paper was soaked in a 10 μM iron(III) chloride solution and then dried. In the presence of hydrazoic acid, the color changes from yellow to a bright red. See: Feigl, F. *Spot Tests in Organic Analysis*; Elsevier Scientific Publishing Co.: Amsterdam, 1975. Above a 1 M aqueous solution of sodium azide at reflux, the strip turned red slowly over about 10 s, and using the 0.5 M azide modification no hydrazoic acid was detected. In contrast, above the 1 M solution of sodium azide and 0.5 M $ZnBr_2$ in DMF at 100 °C, the strip turned bright red before it could even be inserted in the flask.

(18) Flippin, L. *Tetrahedron Lett*. **1991**, *47*, 6857−6860.

Table 2. Other Tetrazoles

Entry	Tetrazole[a]	temp. time	Yield	m.p.
2k		170°C 24hr	82%	36-38°C
2l		170°C 24hr	75%	146°C
2m[b]		reflux 36hr	82%	162-163°C
2n[b]		reflux 24hr	89%	178-179°C
2o		reflux 24hr	89%	178-179°C
2p		reflux 48hr	79%	155-156°C
2q		reflux 48hr	64%	deflagration at 273°C
2r[b]		reflux 24hr	57%	150-151°C
2s		reflux 24hr	89%	150-151°C
2t[b]		reflux 6hr	72%	120-122°C

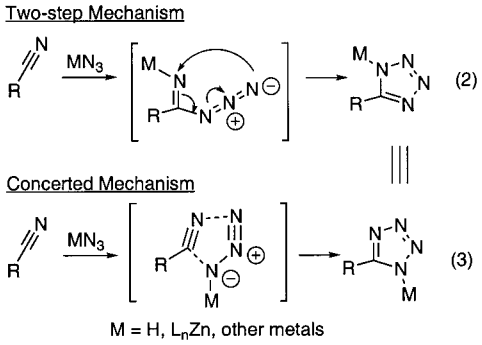
[a] These reactions were run on 20 mmol scale. [b] These reactions were run with ^{i}PrOH as a cosolvent (10% v/v).

drawing substituents at the α-position (**1m**,**n**), temperatures can be lower. At one extreme, trifluoroacetonitrile has been shown to react rapidly with sodium azide in acetonitrile solution at room temperature in the absence of any catalyst.[19] Alkyl nitriles with a hydroxy group at the α-position (**1o**) also proceed at lower temperatures; in the analogous case with an amino group in place of the hydroxy group the reaction proceeded well, but purification was very difficult. Presumably, this acceleration is due to a combination of the substituents' intramolecular hydrogen bonding and *σ*-electronic effects. Some α,*β*-unsaturated vinyl nitriles (**1p**,**q**) are good substrates, but simple alkylacrylonitrile derivatives only decomposed under the reaction conditions and the tetrazoles were not detected. Thiocyanates gave the 5-thiotetrazoles **2r** and **2s**, and a dialkylated cyanamide also reacted, furnishing the 5-aminotetrazole **2t**. Nitriles attached to oxygen, as in cyanates (ROCN), have been shown to react with sodium azide in water at room temperature in the absence of catalyst.[20]

Kinetic studies using the water-soluble nitrile **1i** revealed first-order dependence in both nitrile and azide and one-half order dependence for zinc bromide. The mechanism of the addition of hydrazoic acid/azide ion to a nitrile to give a tetrazole has been debated, with evidence supporting both a two-step mechanism[8b,21] and

(19) Norris, W. P. *J. Org. Chem.* **1962**, *27*, 3248−3251.
(20) Grigat, E.; Pütter, R.; Mühlbauer, E. *Chem. Ber.* **1965**, *12*, 3777−3785.

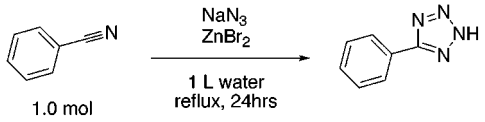
Chart 1



a concerted [2 + 3] cycloaddition[22] (Chart 1, eq 2). Our mechanistic studies to date imply that the role of zinc is not simply that of a Lewis acid; a number of other Lewis acids were tested and caused little to no acceleration of the reaction.[23] In contrast, Zn^{2+} exhibited a 10-fold rate acceleration at 0.03 M, which corresponds to a rate acceleration of approximately 300 at the concentrations typically used. The exact role of zinc is not yet clear.

Empirically, we found that to ensure complete reaction one needs a 0.5 molar equiv of the zinc salt (ZnX_2); however, in many cases, lower loadings of zinc may be used.[24] The chief competing reaction is hydrolysis of the nitrile to the primary amide; therefore, in cases where the tetrazole-forming reaction is sufficiently fast, namely with electron-poor nitriles, lower zinc loadings did not entail significant formation of the amide byproduct. Other zinc salts such as zinc perchlorate and zinc triflate also work; zinc chloride, while less expensive, led to more of the amide byproduct. Zinc bromide was chosen as the best compromise between cost, selectivity, and reactivity (see Table 3).

Table 3. Mole-Scale Reactions



entry	NaN_3 (mol)	ZnX_2 (0.50 mol)	yield (g)
1	1.05	$ZnCl_2$	98.0 (67%)
2	1.05	$Zn(ClO_4)_2$	101.2 (70%)
3	1.05	$ZnBr_2$	111.1 (76%)
4	1.50	$ZnBr_2$	135.2 (93%)

The process became even more attractive for large-scale applications when we found that it could be run at higher concentration without sacrificing yield and without the use of organic solvents in the workup or isolation phases. The resulting products were spectroscopically identical by ^{1}H NMR and ^{13}C NMR to those synthesized by the general method outlined below; however, the melting points were slightly lower.

(21) Jursic, E.; Zdravkovski, Z. *THEOCHEM* **1994**, *118*, 11−22.
(22) (a) Titova, I. E.; Poplavskii, V. S.; Koldobskii, G. I.; Ostrovskii, V. A.; Nikolaev, V. D.; Erusalimskii, G. B. *Khim. Geterosikl. Soedin.* **1986**, *8*, 1086−1089. (b) Ostrovskii, V. A.; Poplavskii, V. S.; Koldobskii, G. I.; Erusalimskii, G. B. *Khim. Geterosikl. Soedin.* **1992**, *9*, 1214−1219.
(23) Some of the metals tested include Li, K, Cs, Mg, Ca, Ba, Fe, Co, Ni, Cu, Ag, Zn, Ce, Sm, Yb, B, Al, and Bi.
(24) We found that heterocyclic nitriles would proceed to completion, albeit in lower yields, with only sodium azide in refluxing water (Epple, R., unpublished work) but that zinc was necessary to coax the majority of nitriles into reacting with azide.

In summary, we have demonstrated an exceedingly simple protocol for transforming a wide variety of nitriles into the corresponding 1*H*-tetrazoles. By using zinc salts as catalysts, we showed that water can be used as the solvent despite the relative insolubility of the starting materials. This discovery should facilitate the preparation of tetrazoles in the laboratory.

Experimental Section

All ^{1}H NMR spectra taken on a Bruker AMX-400 spectrometer in DMSO-d_6 with DMSO as a standard at 2.50 ppm. All ^{13}C NMR spectra taken on the same machine at 100 MHz in DMSO-d_6 with DMSO as a standard at 39.50 ppm, unless otherwise noted. All melting points were taken on a Thomas-Hoover Uni-melt melting point apparatus. Reagents were used unpurified, and deionized water was used as solvent.

Large-Scale, Organic Solvent Free Procedure for the Synthesis of Tetrazoles. To a three-necked 3 L round-bottomed flask equipped with a mechanical stirrer was added benzonitrile (103.1 g, 1.00 mol), 1 L of water, sodium azide (68.2 g, 1.05 mol), and 68.1 g. (0.50 mol) zinc chloride. The reaction was refluxed in a hood, but open to the atmosphere, for 24 h with vigorous stirring. After the mixture was cooled to room temperature, the pH was adjusted to 1.0 with concentrated HCl (~120 mL), and the reaction was stirred for 30 min to break up the solid precipitate, presumably $(PhCN_4)_2$-Zn. The new precipitate was then filtered, washed with 2 × 200 mL of 1 N HCl, and dried in a drying oven at 90 °C overnight to give 98.0 g of 5-phenyltetrazole as a white powder (67% yield, mp 211 °C (lit.[25] mp 216 °C)).

General Procedure for the Transformation of Nitriles into Tetrazoles. To a 250 mL round-bottomed flask was added the nitrile (20 mmol), sodium azide (1.43 g, 22 mmol), zinc bromide (4.50 g, 20 mmol), and 40 mL of water.[26] The reaction mixture was refluxed for 24 h; vigorous stirring is essential. HCl (3 N, 30 mL) and ethyl acetate (100 mL) were added, and vigorous stirring was continued until no solid was present and the aqueous layer had a pH of 1. If necessary, additional ethyl acetate was added. The organic layer was isolated and the aqueous layer extracted with 2 × 100 mL of ethyl acetate. The combined organic layers were evaporated, 200 mL of 0.25 N NaOH was added, and the mixture was stirred for 30 min, until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered, and the solid washed with 20 mL of 1 N NaOH. To the filtrate was added 40 mL of 3 N HCl with vigorous stirring causing the tetrazole to precipitate. The tetrazole was filtered and washed with 2 × 20 mL of 3 N HCl and dried in a drying oven to furnish the tetrazole as a white or slightly colored powder.

Modifications. For tetrazoles that do not show significant reaction after 1 day at reflux, the reaction is run in a pressure tube submerged up to the neck in an oil bath at 140 °C or, if necessary, 170 °C. In either case, if the extent of reaction is less than 50% after 1 day, it is continued for an additional 1 day. The times given for reaction may be slightly longer than necessary, but not more than twice the time needed. As the tetrazole products are quite stable, no decrease in yield was observed from excess reaction times, so the times were not optimized beyond a factor of 2. If, during the reaction, the nitrile is not dispersed well (e.g., nitrile clumps up), 5−10 mL of ^{i}PrOH is added to the reaction mixture. In cases where a basic nitrogen was present in the molecule, the initial acidification and extraction into ethyl acetate was foregone, and the final acidification was only taken to pH 6.5, at which point the zwitterion precipitated. If little or no precipitate was formed upon final acidification, the aqueous layer was saturated with NaCl and extracted with 3 × 100 mL of ethyl acetate; the organic layer was dried with sodium sulfate and evaporated to dryness. In some cases, extremely nonpolar tetrazoles may require column purification. Modifications to the general method are given for individual tetrazoles below.

5-Phenyltetrazole (2a). The product **2a** (2.20 g; 75% yield) had the following data: mp 215−216 °C; ^{1}H NMR 8.04 (m, 2H), 7.61 (m, 3H); ^{13}C NMR 155.2 (br), 131.28, 129.45, 127.02, 124.17; HRMS (MALDI) calcd for $C_7H_7N_4$ (MH^+) 147.0665, found 147.0666. Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: C, 57.65; H, 4.17; N, 38.04.

5-(4-Nitrophenyl)tetrazole (2b). The product **2b** (3.42 g; 94% yield) had the following data: mp 220 °C; ^{1}H NMR 8.44 (m, 2H), 8.29 (m, 2H); ^{13}C NMR 155.4 (br), 148.74, 130.60, 128.22, 124.64; HRMS (MALDI) calcd for $C_7H_4N_5O_2$ $(M - H)^-$ 190.0360, found 190.0363. Anal. Calcd for $C_7H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64. Found: C, 44.10; H, 2.63; N, 36.37.

5-(4-Methoxyphenyl)tetrazole (2c). The reaction was refluxed for 48 h. The product **2c** (3.04 g; 86% yield) had the following data: mp 231−232 °C; ^{1}H NMR 7.97 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.8 Hz), 3.83 (s, 3H); ^{13}C NMR 161.47, 154.6 (br), 128.66, 116.28, 114.86, 55.45; HRMS (MALDI) calcd for $C_8H_9N_4O$ (MH^+) 177.0771, found 177.0777.

5-(2-Pyridyl)tetrazole (2d). Workup excluded initial acidification and extraction; the reaction mixture was simply basified by addition of 2.5 equiv of NaOH, filtered, acidified to pH = 6.5, and filtered, and the solid was washed with water. The product **2d** (2.31 g; 79% yield) had the following data: mp 211 °C; ^{1}H NMR 8.79 (m, 1H), 8.22 (d, 1H, J = 7.6 Hz), 8.08 (m, 1H), 7.62 (m, 1H); ^{13}C NMR 154.9 (br), 150.10, 143.76, 138.29, 126.11, 122.62; HRMS (MALDI) calcd for $C_6H_6N_5$ (MH^+) 148.0618, found 149.0617.

5-Pyrazinetetrazole (2e). Workup excluded initial acidification and extraction; the reaction mixture was simply basified by addition of 2.5 equiv of NaOH, filtered, acidified to pH = 6.5, and filtered, and the solid was washed with water. The product **2e** (2.44 g; 83% yield) had the following data: mp 193−195 °C; ^{1}H NMR 9.38 (m, 1H), 8.82 (m, 1H), 8.58 (br, 1H); ^{13}C NMR 154.9 (br), 146.83, 143.93, 143.07, 140.37; HRMS (MALDI) calcd for $C_5H_5N_6$ (MH^+) 149.0570, found 149.0569.

5-(4-Hydroxyphenyl)tetrazole (2f). The reaction mixture was stirred in a pressure tube submerged in an oil bath at 140 °C. The product **2f** (3.11 g; 96% yield) had the following data: mp 234−236 °C; ^{1}H NMR 10.20 (br, 1H), 7.86 (d, 2H, J = 8.5 Hz), 6.95 (d, 2H, J = 8.5 Hz); ^{13}C NMR 160.22, 154.7 (br), 128.89, 116.25, 114.68; HRMS (MALDI) calcd for $C_7H_7N_4O$ (MH^+) 163.0614, found 163.0612.

5-(2-Naphthyl)tetrazole (2g). The reaction mixture was stirred in a pressure tube submerged in an oil bath at 140 °C for 48 h. The product **2g** (2.85 g; 73% yield) had the following data: mp 205−207 °C; ^{1}H NMR 8.67 (m, 1H), 8.12 (m, 2H), 8.06 (m, 1H), 7.99 (m, 1H), 7.61 (m, 2H); ^{13}C NMR 155.5 (br), 133.89, 132.59, 129.19, 128.63, 127.89, 127.86, 127.27, 127.04, 123.69, 121.54; HRMS (MALDI) calcd for $C_{11}H_9N_4$ (MH^+) 197.0822, found 197.0829.

1,2-Bis(5-tetrazolyl)benzene (2h). The reaction mixture was refluxed for 48 h. The product **2h** (2.75 g; 64% yield) had the following data: mp 228−230 °C; ^{1}H NMR 7.89 (m, 2H), 7.82 (m, 2H); ^{13}C NMR 154.8 (br), 131.37, 130.78, 124.53; HRMS (MALDI) calcd for $C_8H_6N_8Na$ (MNa^+) 237.0608, found 237.0609.

4-(5-Tetrazolyl)(2-hydroxyethyloxy)ethylbenzamide (2i). After final acidification, reaction mixture was set aside until product crystallized from the solution (~2 days). The product **2i** (3.35 g; 67% yield) had the following data: mp 158−160 °C; ^{1}H NMR 8.69 (t, 1H, J = 5.2 Hz), 8.13 (d, 2H, J = 8.5 Hz), 8.05 (d, 2H, J = 8.5 Hz), 3.56 (t, 2H, J = 5.6 Hz), 3.51 (m, 2H), 3.46 (m, 2H); ^{13}C NMR 165.60, 155.0 (br), 136.70, 128.32, 126.61, 72.24, 68.91, 68.89, 60.32; HRMS (MALDI) calcd for $C_{12}H_{15}N_5O_3Na$ (MNa^+) 300.1067, found 300.1059.

5-(2-(4′-Methyl)biphenyl)tetrazole (2j). The reaction was stirred in a pressure tube submerged in an oil bath at 170 °C for 48 h. Silica gel column chromatography was used to purify

(25) Note that the literature melting point of 216 °C was obtained when the general procedure outlined in the Experimental Section, which includes an organic extraction, was used.

(26) As mentioned in the text, the 1:1 molar ratio of $NaN_3/ZnBr_2$ is more general. Note that the four 1.0 M scale reactions run with benzonitrile (vide supra) were all performed with a NaN_3/ZnX_2 molar ratio of 2:1.

the final product. The product **2j** (3.16 g; 67% yield) had the following data: mp 150 °C; ^{1}H NMR 7.66 (m, 2H), 7.55 (m, 2H), 7.11 (d, 2H, J = 7.9 Hz), 6.97 (d, 2H, J = 7.9 Hz), 2.28 (s, 3H); ^{13}C NMR 154.8 (br), 141.51, 136.81, 136.32, 131.12, 130.63, 130.56, 128.94, 128.68, 127.56, 123.36, 20.65; HRMS (MALDI) calcd for $C_{14}H_{13}N_4$ (MH^+) 237.1135, found 237.1142.

5-*n*-Heptyltetrazole (2k). The reaction was stirred in a pressure tube submerged in an oil bath at 170 °C. Upon final acidification, the product separated as an oil; after addition of NaCl, the aqueous layer was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to give the crude product, which was purified by column chromatography. The product **2k** (2.75 g.; 82% yield) had the following data: mp 36−38 °C; ^{1}H NMR ($CDCl_3$, using TMS as a standard at 0.0 ppm) 3.12 (t, 2H, J = 7.6 Hz), 1.88 (m, 2H), 1.43−1.22 (m, 8H), 0.83 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$ using $CDCl_3$ as a standard at 77.0 ppm) 156.9, 31.52, 28.94, 28.70, 27.65, 23.42, 22.51, 13.99; HRMS (MALDI) calcd for $C_8H_{17}N_4$ (MH^+) 169.1448, found 169.1451.

5-Methyltetrazole (2l). The reaction mixture was stirred in a pressure tube submerged in an oil bath at 170 °C. Upon completion of the reaction, the product was made basic with 2.5 equiv of 1 N NaOH, stirred, and filtered. Following acidification with HCl, the solution was saturated with magnesium sulfate and extracted with 6 × 200 mL ethyl acetate, which was dried and evaporated to give the crude product. The product **2l** (1.37 g; 75% yield) had the following data: mp 146 °C; ^{1}H NMR 2.48 (s, 3H); ^{13}C NMR 152.2 (br), 8.43. Anal. Calcd for $C_2H_4N_4$: C, 28.57; H, 4.79; N, 66.63. Found: C, 28.49; H, 4.61; N, 62.76.

5-(2-(*N*-Benzylacetamido)tetrazole (2m). 2-Propanol (5 mL) was added to the reaction mixture to facilitate dispersal of the nitrile. Due to relative insolubility of the tetrazole in alkaline water, the initial organic extracts were combined, dried (Na_2SO_4), and evaporated to give the product. The product **2m** (3.55 g; 82% yield) had the following data: mp 162−163 °C; ^{1}H NMR 8.85 (br, 1H), 7.36−7.23 (m, 5H), 4.33 (d, 2H, J = 5.56 Hz), 3.98 (s, 2H); ^{13}C NMR 166.21, 151.10 (br), 138.92, 128.43, 127.44, 127.05, 42.57, 30.56; HRMS (MALDI) calcd for $C_{10}H_{12}N_5O$ (MH^+) 218.1036, found 218.1041.

2,2-Bis(5-tetrazolyl)propane (2n). 2-Propanol (5 mL) was added to the reaction mixture to facilitate dispersal of the nitrile. Upon final acidification, the product separated as an oil; after addition of NaCl, the aqueous layer was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to give the product. The product **2n** (3.20 g; 89% yield) had the following data: mp 178−179 °C; ^{1}H NMR 1.87 (s, 6H); ^{13}C NMR 160.9 (br), 33.21, 26.70; HRMS (MALDI) calcd for $C_{14}H_{13}N_4$ $(M - H)^-$ 179.0799, found 179.0800.

5-(Hydroxybenzyl)tetrazole (2o). Upon final acidification, the product separated as an oil; after addition of NaCl, the aqueous layer was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to give the product. The product **2o** (3.14 g; 89% yield) had the following data: mp 178−179 °C; ^{1}H NMR 7.44 (m, 2H), 7.37 (m, 2H), 7.30 (m, 1H), 6.81 (br, 1H), 6.15 (s, 1H); ^{13}C NMR 159.2 (br), 140.99, 128.49, 128.05, 126.44, 66.46; HRMS (MALDI) calcd for $C_8H_8N_4ONa$ (MNa^+) 199.0590, found 199.0596.

Cinnamyltetrazole (2p). The reaction was refluxed for 48 h. The product **2p** (2.71 g; 79% yield) had the following data: mp 155−156 °C; ^{1}H NMR 7.71 (m, 2H), 7.65 (d, 1H, J = 16.7 Hz), 7.46−7.36 (m, 3H), 7.33 (d, 1H, J = 16.7 Hz); ^{13}C NMR 154.1 (br), 137.85, 134.88, 129.63, 128.99, 127.49, 110.41; HRMS (MALDI) calcd for $C_9H_9N_4$ (MH^+) 173.0822, found 173.0829.

Fumaryltetrazole (2q). The reaction was refluxed for 48 h. The product **2q** (2.10 g; 64% yield) deflagrated at 273 °C: ^{1}H NMR 7.65 (s, 2H); ^{13}C NMR 153.4 (br), 119.51; HRMS (MALDI) calcd for $C_4H_3N_8$ $(M - H)^-$ 163.0486, found 163.0488.

5-(Benzylthio)tetrazole (2r). 2-Propanol (5 mL) was added to the reaction mixture to facilitate dispersal of the nitrile. The product **2r** (2.19 g; 57% yield) had the following data: mp 150−151 °C; ^{1}H NMR 7.39 (m, 2H), 7.34−7.24 (m,

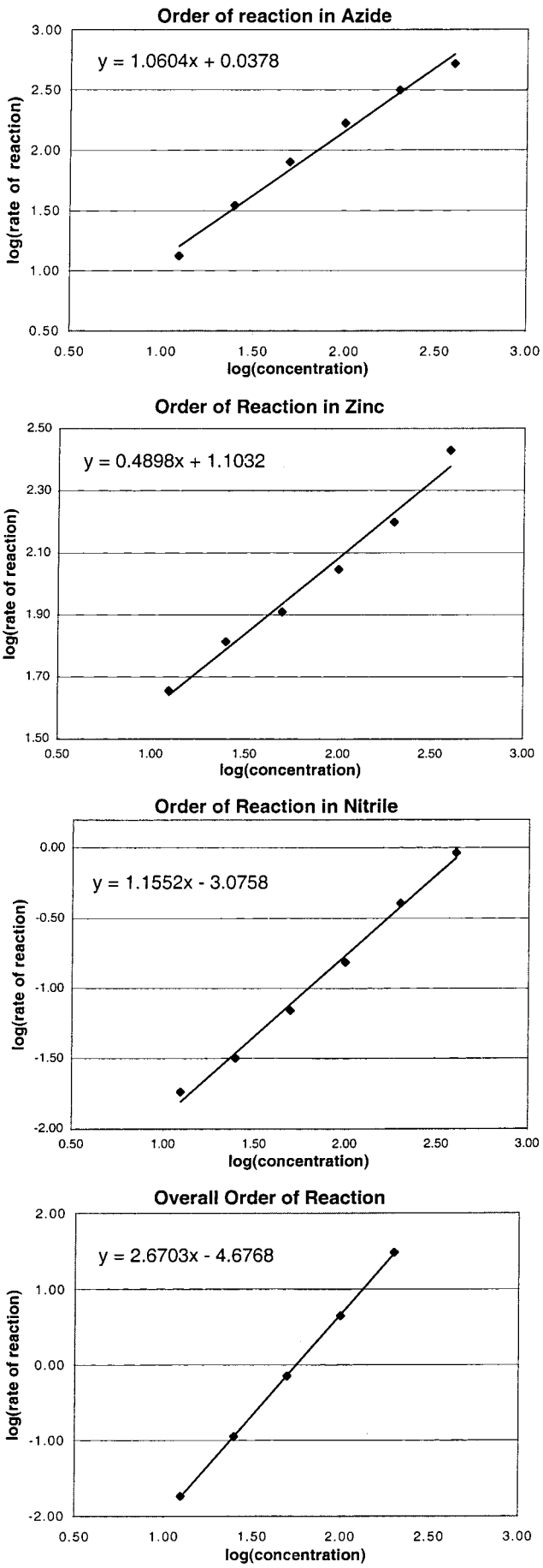


Figure 1. Order of reaction in azide, zinc, and nitrile and overall order of reaction.

3H), 4.50 (s, 2H); ^{13}C NMR 153.7 (br), 136.70, 128.93, 128.58, 127.67, 35.98; HRMS (MALDI) calcd for $C_8H_9N_4S$ (MH^+) 193.0542, found 193.0539.

5-(Methylthio)tetrazole (2s). Upon final acidification, the product separated as an oil; after addition of NaCl, the aqueous layer was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to give the product. The product **2s** (2.07 g; 89% yield) had the following data: mp 150−151 °C; ^{1}H NMR 2.69 (s, 3H); ^{13}C NMR 155.1 (br), 14.43. Anal. Calcd for $C_2H_4N_4S$: C, 20.68; H, 3.47; N, 47.61. Found: C, 20.89; H, 3.40; N, 47.61.

5-(Diethylamino)tetrazole (2t). Glycerol (5 mL) was added to the reaction mixture to facilitate dispersal of the nitrile. Upon final acidification, the product separated as an oil; after addition of NaCl, the aqueous layer was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated to give the product. The product **2t** (1.99 g; 72% yield) had the following data: mp 120−122 °C; ^{1}H NMR 3.37 (q, 2H, J = 7.0 Hz), 1.09 (t, 3H, J = 7.0 Hz); ^{13}C NMR 157.4 (br), 43.38, 12.69; HRMS (MALDI) calcd for $C_5H_{12}N_5$ (MH^+) 142.1087, found 142.1089.

4-Cyano(2-hydroxyethyloxy)ethylbenzamide (1i). A 500 mL round-bottomed flask was charged with a stir bar, 4-cyanobenzoic acid (14.7 g., 100 mmol), and 100 mL of CH_2Cl_2. To the stirring suspension were added oxalyl chloride (12 mL, 135 mmol) and a catalytic amount of dimethyl formamide (200 μL). After 2 h, the suspended solid had dissolved; to this mixture was slowly added a solution of 2-(2-aminoethoxy)-ethanol (11.55 g, 110 mmol) and sodium carbonate (12.5 g, 120 mmol) in 100 mL of water. After 1 h, the organic layer was separated, and the aqueous layer was acidified to a pH of 1 with 3 N HCl, saturated with magnesium sulfate, and extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution (20 mL) and 3 N HCl (20 mL), dried with sodium sulfate, and evaporated to give **1i** (22.9 g; 98% yield) as a light yellow solid. The product had the following data: mp 85−86 °C; ^{1}H NMR 8.78 (t, 1H, J = 5.6 Hz), 7.99 (d, 2H, J = 8.5 Hz), 7.95 (d, 2H, J = 8.5 Hz), 4.61 (br, 1H), 3.54 (t, 2H, J = 5.6 Hz), 3.49 (m, 2H), 3.44 (m, 4H); ^{13}C NMR 164.95, 138.40, 132.45, 128.08, 118.39, 113.58, 72.17, 68.71 (2), 60.22; HRMS (MALDI) calcd for $C_{12}H_{14}N_2O_3Na$ (MNa^+) 257.0897, found 257.0899.

Kinetic Studies. Aqueous solutions (2 mL) of the three reactants in appropriate proportions were prepared. To measure the individual orders of reaction, the concentration of the target reactant was varied from 400 to 12.5 mM in factors of 2, while the other reagents were both held constant at 50 mM. For the overall reaction, the reactants were all varied from 400 to 12.5 mM in factors of 2.

The vials were placed in a heating block set to 90 °C, and at regular intervals 100 μL aliquots were taken out and diluted 10-fold with a solution of 50% acetonitrile and 50% 0.2 N aqueous HCl. These samples were then analyzed by LCMS and calibrated using samples of known concentration. The rates of reaction were calculated from only those data points corresponding to reactions that were less than 10% complete. The log of the rates were then plotted against the log of the concentrations for each series, and the slopes were calculated by linear regression to give the order of the reaction. These plots are shown in Figure 1.

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Supporting Information Available: The data points and analysis for the kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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