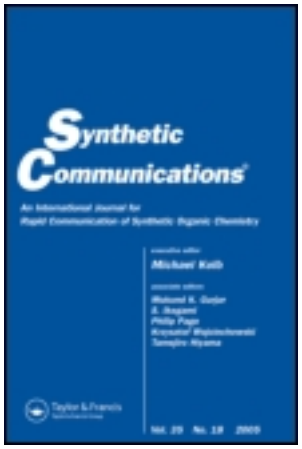


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Amine Salt-Catalyzed Synthesis of 5-Substituted 1H-Tetrazoles from Nitriles

Yi Zhou [a b], Cheng Yao [a], Renjie Ni [a] & Gaowen Yang [b]

[a] Department of Applied Chemistry, College of Science, Nanjing University of Technology, Nanjing, China

[b] Jiangsu Laboratory of Advanced Functional Materials, Changshu Institute of Technology, Changshu, China

Version of record first published: 05 Aug 2010.

To cite this article: Yi Zhou , Cheng Yao , Renjie Ni & Gaowen Yang (2010): Amine Salt-Catalyzed Synthesis of 5-Substituted 1H-Tetrazoles from Nitriles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:17, 2624-2632

To link to this article: http://dx.doi.org/10.1080/00397910903318583

*Synthetic Communications*®, 40: 2624–2632, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903318583

Taylor & Francis
Taylor & Francis Group



# AMINE SALT–CATALYZED SYNTHESIS OF 5-SUBSTITUTED 1*H*-TETRAZOLES FROM NITRILES

**Yi Zhou,[1,2] Cheng Yao,[1] Renjie Ni,[1] and Gaowen Yang[2]**

[1]*Department of Applied Chemistry, College of Science, Nanjing University of Technology, Nanjing, China*

[2]*Jiangsu Laboratory of Advanced Functional Materials, Changshu Institute of Technology, Changshu, China*

***The [3 + 2] cycloaddition reaction between sodium azide and various organic nitriles proceeds smoothly in the presence of amine salts as catalyst in dimethylformamide. The corresponding 5-substituted 1-H tetrazoles were obtained under mild condition in good to excellent yields. Supplemental materials are available for this article. Go to the publisher's online edition of* Synthetic Communications® *to view the free supplemental file.***

***Keywords***: Amine salt catalyst; azide; [3 + 2] cycloaddition; heterocycles; tetrazole

## INTRODUCTION

Tetrazoles are a class of heterocycles with a wide range of applications, and they are receiving considerable attention.[1] This functional group is regarded as biologically equivalent to the carboxylic acid in medicinal chemistry,[2] such as polydentate aromatic N-donor ligands in coordination chemistry, and in various material sciences, including specialty explosives, information recording systems, and photography.[3,4]

The most widely used method of preparation for 5-substituted 1-*H* tetrazoles is [2 + 3] cycloaddition of azide anion to organic nitriles, and many methods are reported in the literature.[5] The addition of hydrazoic acid to the cyanide group, resulting in the formation of 5-substituted tetrazole derivatives, was first reported in 1932.[6] Currently, the most common methods involves the use of sodium azide in the presence of silicon, tin azide,[7] and ammonium azide ($NH_4Cl$ catalyst).[8] However, each of those protocols has disadvantages, including the use of expensive reagents, toxic metals, drastic reaction conditions, water sensitivity, the presence of dangerous hydrazoic acid, and sublimation of explosive $NH_4N_3$, which is highly dangerous. In addition, the major drawback of these methods is the difficulty of removing the highly toxic residue at the end of the reaction. Sharpless and coworkers recently described a safe, convenient, and environmentally friendly procedure for the

Received March 28, 2009.

Address correspondence to Cheng Yao, Department of Applied Chemistry, College of Science, Nanjing University of Technology, Nanjing 210009, China. E-mail: yaocheng@njut.edu.cn

preparation of 5-substituted 1*H*-tetrazoles, which can be accomplished with water as a solvent and zinc salts as catalyst.[9] However, sterically hindered aromatic or deactivated alkyl nitriles usually require high temperatures (140–170 °C), and it is difficult to completely separate tetrazole coordination polymers.

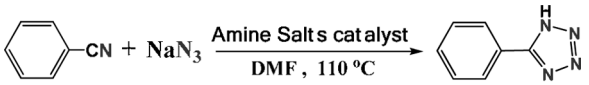
We develop a novel synthetic method that is free from these problems, and can safely proceed for the preparation of tetrazoles on an industrial scale without metallic catalysts. In continuation of our work on tetrazole chemistry, we herein report the synthesis of 5-substituted 1-*H*-tetrazoles from a wide variety of organic nitriles with sodium azide using amine salt catalysts.



## RESULTS AND DISCUSSION

In an effort to develop a better catalytic system, various experimental parameters were carried out in the reaction of benzonitrile **1a** with sodium azide as a model substrate, and the results are summarized in Table 1. First, we examined the effect of amine salt on the reaction. A mixture of **1a**, $NaN_3$, and amine salts in dimethylformamide (DMF) was heated at 110 °C for 8 h with stirring. It was

**Table 1.** Optimization of reaction conditions in amine salt–catalyzed [2 + 3] cycloaddition on the formation of tetrazole 1b from 1a[a]




1a 1b

| Entry | Solvent | Catalyst | Yield (%)[b] |
|---|---|---|---|
| 01 | DMF | Py · HCl | 84 |
| 02 | DMF | $C_6H_5NH_2 \cdot HCl$ | 78 |
| 03 | DMF | $NH_4Cl$ | 86 |
| 04 | DMF | $Et_3N \cdot HCl$ | 76 |
| 05 | DMF | None | 26 |
| 06 | DMF | $(CH_3)_4NBr$ | 63 |
| 07 | DMF | A[c] | 26 |
| 08 | DMF | B[c] | 32 |
| 09 | DMF | C[c] | 61 |
| 10 | DMF | CTAB[d] | 42 |
| 11 | DMF | Py · HCl | 58,93[e] |
| 12 | Water | Py · HCl | 19 |
| 13 | DMSO | Py · HCl | 68 |
| 14 | THF | Py · HCl | 0 |
| 15 | Toluene | Py · HCl | 29 |

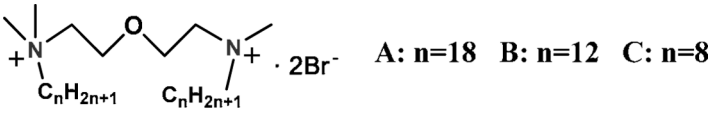
[a]Reaction conditions: benzonitrile (10 mmol), $NaN_3$ (12 mmol, 0.78 g), catalyst (10 mmol), solvent (20 ml), 110 °C, reaction time (8 h).

[b]Yield of isolated products. Structures confirmed by comparison of IR and $^1H$ NMR with those of authentic materials.

[c]Catalyst structure A, B, and C (Scheme 1).

[d]Hexadecyl trimethyl ammonium bromide (CTAB).

[e]Reaction carried out with $NaN_3$ (7 mmol): Py · HCl (10 mmol), yield 58%; $NaN_3$ (12 mmol): Py · HCl (10 mmol), yield 84%; $NaN_3$ (15 mmol): Py · HCl (10 mmol), yield 93%.



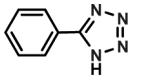
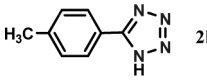
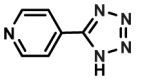
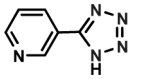
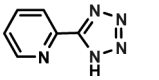
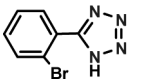
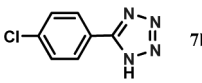
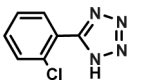
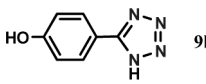
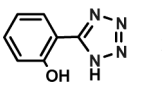
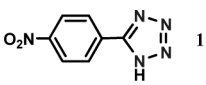
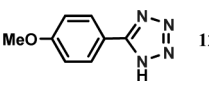
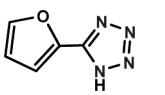

**Scheme 1.** Catalyst structure (A, B, and C).

found that the reactivity of the amine salts differs depending on the structure of the amine. Quaternary amine salts (entries 6 and 10), which had no protons, could catalyze the reaction in poor yields (63% and 42%). Tertiary, secondary, and primary amine salts were better reagents than quaternary amine salts to catalyze the [2 + 3] cycloaddition reaction. When pyridine hydrochloride (Py · HCl; entry 1) and aliphatic amine (entry 4) were compared, the yield for the Py · HCl (yield 84%) was relatively greater for product **1b**. By using $NH_4Cl$ catalyst (yield 86%) in DMF at 110 °C, hydrazoic acid was clearly present in the headspace above the refluxing solvent. In contrast, when the reactions were run with Py · HCl catalyst, no hydrazoic acid could be detected.[10] Furthermore, we synthesized diethyl ether-bis(dimethyl alkyl ammonium bromide) as catalyst (Scheme 1), and the catalytic efficiency decreased with the length of carbochain. Second, the effect of solvent was examined. As shown in Table 1, the reaction proceeded with DMF, $H_2O$, tetrahydrofuran (THF), toluene, and dimethylsulfoxide (DMSO) as the solvent, and it was found that polar organic solvents are more favored. With $H_2O$, THF, and toluene, yields are comparatively poor. Consequently, DMF was chosen as the medium of choice for this cycloaddition. Moreover, production of **1b** was not affected by little water (1–5% volume) in DMF; therefore, recycled DMF and Py, which can be separated from the product without any treatment, can be used for the next reaction only by adding HCl and 0.45 equiv of Py.

For this reaction, the addition of a little excess of $NaN_3$ was essential (entries 1 and 11): by using only 1.2 equiv of $NaN_3$, the yield was a little less (84%) compared to a 93% yield of **1b** when 1.5 equiv of $NaN_3$ was used. After optimized reaction conditions were obtained, we decided to investigate the reaction scope by using the best conditions outlined in Table 1 on a variety of organic nitriles **a** (Table 2) and **c** (Table 3).

The results indicate clearly that this protocol is generally applicable for wide variety of electron-rich and electron-poor aromatic nitriles (Table 2) with $NaN_3$ and that the yields are good. Substrates possessing electron-rich groups on the benzene ring (such as p-$CH_3$, p-OH, and p-$OCH_3$) afford tetrazole products in good yields but require relatively high temperatures and long reaction times. In contrast, arylnitriles having electron-withdrawing groups on the benzene ring (such as *p*-Cl, *p*-$NO_2$, *o*-Cl, and Py groups) react faster and need lower temperatures to give excellent yields. It is noteworthy that electron-poor groups can facility the azide anion attack on the N atom of the cyano group. The present protocol also tolerates many other functional groups as by-products are not observed. It is reported ortho-hydroxy, -chloro, and -bromo benzonitriles are particularly difficult to convert into the corresponding tetrazoles.[11] However, the sterically hindered ortho-substituted aromatic nitriles predictably take longer (18 h) to undergo complete conversion using our protocol. Heteroatom-substituted aromatic nitrile compounds such as

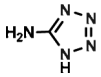
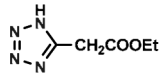
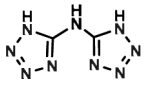
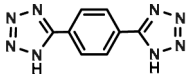
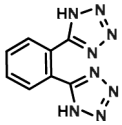
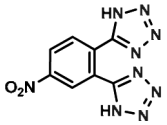
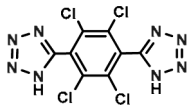
**Table 2.** Synthesis of aromatic 1*H*-tetrazoles[a]

| Entry | Temp (°C)/Time (h) | Product | Yield (%)[b] |
|---|---|---|---|
| **1a** | 110/8 |  **1b** | 84 |
| **2a** | 120/12 |  **2b** | 80 |
| **3a** | 90/8 |  **3b** | 93 |
| **4a** | 110/12 |  **4b** | 79 |
| **5a** | 90/8 |  **5b** | 90 |
| **6a** | 120/18 |  **6b** | 78 |
| **7a** | 110/15 |  **7b** | 89 |
| **8a** | 120/18 |  **8b** | 81 |
| **9a** | 120/18 |  **9b** | 86 |
| **10a** | 120/18 |  **10b** | 79 |
| **11a** | 90/6 |  **11b** | 96 |
| **12a** | 120/24 |  **12b** | 91 |
| **13a** | 100/16 |  **13b** | 89 |

[a]Reaction conditions: aromatic nitrile (10 mmol), $NaN_3$ (12 mmol, 0.78 g), pyridine hydrochloride (0.01 mol, 1.15 g), and DMF (20 ml).

[b]Yield of isolated products.

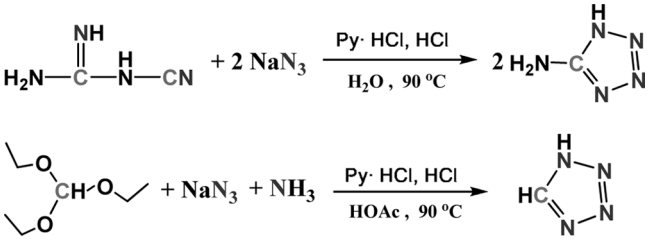
**Table 3.** Synthesis of other 1*H*-tetrazoles[a]

| Entry | Temp (°C)/Time (h) | Product | | Yield (%)[b] |
|---|---|---|---|---|
| **1c** | 90/12 |  | **1d** | 16,71[c] |
| **2c** | 90/12 |  | **2d** | 67,89[d] |
| **3c** | 90/12 |  | **3d** | 86 |
| **4c** | 100/24 |  | **4d** | 81[d] |
| **5c** | 120/18 |  | **5d** | 92 |
| **6c** | 120/18 |  | **6d** | 76 |
| **7c** | 90/12 |  | **7d** | 96 |
| **8c** | 120/24 |  | **8d** | 32 |

[a]Reaction conditions: nitrile (10 mmol), pyridine hydrochloride (0.01 mol, 1.15 g), and $NaN_3$ (12 mmol, 0.78 g) in DMF (20 ml) for **1c–3c**, $NaN_3$ (30 mmol, 1.95 g) in DMF (30 ml) for **5c–8c**.
[b]Isolated yield.
[c]Glacial acetic acid (30 ml) as solvent.
[d]Water (30 ml) as solvent.

2,4-cyanopyridine and 2-furancarbonitrile react smoothly with $NaN_3$ to give products in excellent yields. Control experiments suggest that among 2,3,4-cyanopyridines, the cycloaddition proceeds readily with 2,4-cyanopyridine but is inert with 3-cyanopyridine.

Our method is complementary to that which uses zinc salts as catalyst.[9b] We have been able to achieve good yields with dicyano derivative compounds (Table 3). This reaction provided good to excellent yields for **4d**–**7d**. An electron-poor arylnitrile, 4-nitrophthalonitrile, provided a yield of 96% (**7d**) for this reaction, and 1,2-dicyanobenzene, an hindered arylnitrile, gave a yield of 76% (**6d**). Regrettably,




**Scheme 2.** Synthesis of 1*H*-tetrazole and 5-amino-1*H*-tetrazole.



in this way, the cycloaddition product of more hindered tetrachloroterephthalonitrile **8c** could not be obtained with good yields under our standard conditions and was not pure. The most widely used method to synthesize 1*H*-tetrazole **1c** is cycloaddition of azide to toxic HCN. We changed the solvent from DMF to acetic acid in our catalytic system, and the product was obtained in 71% yield (Scheme 2).

A plausible two-step mechanism (Fig. 1) for the addition of hydrazoic acid/azide anion to a nitrile is proposed in accordance with previous reports.[9e,12] First, Py · HCl reacts with $NaN_3$ to produce Py · $HN_3$ and is polarized as $PyH^+$ and $N_3^-$. Subsequent [2 + 3] cycloaddition between the triple bond of nitrile and $N_3^-$ takes place readily to form the Py · tetrazole intermediate. After the addition of water, the intermediate can be resolved into amine salt and the product. Because of the low pKa (3–5) value of tetrazoles and their highly crystalline nature,[1b,9d] we can use an acid/base system to purify the product. The high-performance liquid chromatography (HPLC) trace (see supporting information available online) showed that the reactant $PyH^+$ was quite stable, and no decrease was observed after reacting for 8 h. It should be noted that Py · HCl only reacts with 1 equivalent of the substrate because $PyH^+$ can make the tetrazole anion stable, and it cannot be recycled in the system. DMF and Py could be recovered in alkaline condition and recycled without

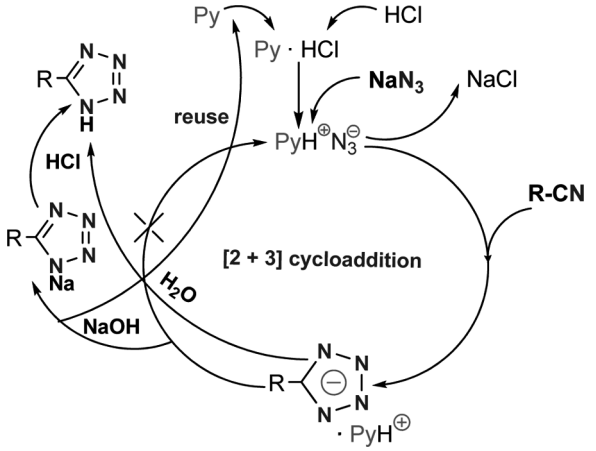



**Figure 1.** Proposed mechanism for Py · HCl-catalyzed synthesis of 5-substituted 1*H*-tetrazoles.

any further treatment on an industrial scale or recovered by only simple distillation, and the NaCl waste could be easily disposed.

## CONCLUSIONS

In conclusion, we have described a useful and convenient method for the synthesis of 1*H*-tetrazole products, which provides good yields under mild conditions. This catalytic system is not only capable of processing a wide range of aryl and other nitriles in cycloaddition but also tolerates a broad range of a series of functional groups. This method may provide an excellent opportunity for parallel synthesis and industrial production of 5-substituted 1*H*-tetrazoles, despite the limiting use of DMF as solvent. It can also provide a method for the synthesis of 5-substituted 1*H*-tetrazole products from aldehydes without preparation of nitrile compounds from halides and toxic cyanides.



## EXPERIMENTAL

### Typical Procedure for Transformation of Nitriles into 5-Substituted 1*H*-Tetrazoles

Nitrile (10 mmol), $NaN_3$ (12 mmol, 0.78 g), and Py · HCl (10 mmol, 1.15 g) in 20 mL of DMF were added to a 50-mL round-bottomed flask. The reaction mixture was heated at 110 °C for 8 h with vigorous stirring. Conversion was monitored by HPLC and thin-layer chromatography (TLC). After that, the reaction mixture was cooled to room temperature and dissolved in 4 mL of NaOH aqueous solution (5 M) with 30 min of stirring. The solution was concentrated under reduced pressure by the removal of DMF and Py; the reaction residue was dissolved in 10 mL water. The pH value was adjusted to 1 with HCl (3 M, 10 mL) to form a precipitate. The precipitate was then filtered, washed with $2 \times 10$ mL of 3 M HCl, and dried at 80 °C overnight to furnish pure 5-phenyl-1-*H*-tetrazole **1b** as a white solid (1.23 g) in 84% yield (mp 216–218 °C).

### 5-Phenyl-1*H*-tetrazole (1b)

$^1$H NMR (500 MHz, DMSO-$d_6$) δ: 8.04 (m, 2H), 7.63 (m, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 131.3, 129.5, 127.0, 124.2; IR (neat): 3207, 3000–2400, 1611, 1562, 1493, 1466, 688 $cm^{-1}$; FAB-MS: $m/z$ 146.0 ($M^+$). Crystal data for **1b** ($C_7H_6N_4$): Mr = 146.16, orthorhombic, space group Ama2, a = 9.810(4) Å, b = 15.257(7) Å, c = 4.546(2) Å, V = 680.4(5) $Å^3$, Z = 4, $R_1 = 0.0302$, $wR_2 = 0.0658$ [$I > 2\sigma(I)$], $\rho_{cal.} = 1.427$ g/$cm^3$, $T = 291(2)$ K, crystal dimensions $0.16 \times 0.12 \times 0.10$ $mm^3$.

## ACKNOWLEDGMENTS

We thank the State Key Laboratory of Materials-Oriented Chemical Engineering Foundation support of this work. We also thank Xiaoming Ren for his important contribution in the sample analysis of this work.

## REFERENCES


1. (a) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky, C. W. Rees, E. F. V. Scriven (Eds.); Pergamon: Oxford, UK, 1996; vol. 4; (b) Valentina, A.; Gottfried, S. 1,3-Dipolar cycloaddition: Click chemistry for the synthesis of 5-substituted tetrazoles from organoaluminum azides and nitriles. *Angew. Chem., Int. Ed.* **2007**, *46*, 8440–8444.
2. (a) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. Medicinal chemistry of tetrazoles. *Prog. Med. Chem.* **1980**, *17*, 151–183; (b) Juby, P. F.; Hudyma, T. W.; Brown, M. Steroids, CCCX: Structure–activity relation of some steroidal hypnotic agents. *J. Med. Chem.* **1968**, *11*, 111–117.
3. (a) Wang, L. Z.; Qu, Z. R.; Zhao, H.; Wang, X. S.; Xiong, R. G.; Xue, Z. L. Isolation and crystallographic characterization of a solid precipitate/intermediate in the preparation of 5-substituted 1H-tetrazoles from nitrile in water. *Inorg. Chem.* **2003**, *42*, 3969–3971; (b) Dinca, M.; Dailly, A.; Liu, Y.; Brown, C. M.; Neumann, D. A.; Long, J. R. Hydrogen storage in a microporous metal–organic framework with exposed $Mn^{2+}$ coordination sites. *J. Am. Chem. Soc.* **2006**, *128*, 16876–16883.
4. (a) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. Chemistry and properties: Reviews and accounts on heterocyclic chemistry. *Targets Heterocycl. Syst.* **1999**, *3*, 467–526; (b) Koldobskii, G. I.; Ostrovskii, V. A. Tetrazoles. *Usp. Khim.* **1994**, *63*, 797–814.
5. (a) Curran, D. P.; Hadida, S.; Kim, S.-Y. Tris(2-perfluorohexylethyl)tin azide: A new reagent for preparation of 5-substituted tetrazoles from nitriles with purification by fluorous/organic liquid–liquid extraction. *Tetrahedron* **1999**, *55*, 8997–9006; (b) Duncia, J. V.; Pierce, M. E.; Santella, J. B. Three synthetic routes to a sterically hindered tetrazole: A new one-step mild conversion of an amide into a tetrazole. *J. Org. Chem.* **1991**, *56*, 2395–2400; (c) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. Novel synthesis of 5-substituted tetrazoles from nitriles. *Synthesis* **1998**, 910–914; (d) Valentina, A.; Gottfried, S. 1,3-Dipolar cycloaddition: Click chemistry for the synthesis of 5-substituted tetrazoles from organoaluminum azides and nitriles. *Angew. Chem., Int. Ed.* **2007**, *46*, 8440–8444.
6. (a) Braun, J.; Keller, W. Synthese von Tetrazol-Verbindungen aus Säurenitrilen. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1677–1685; (b) Robert, M. H.; Charles, F. F. Synthesis of iminotetrazoline derivatives as trichomonacidal and fungicidal agents. *J. Org. Chem.* **1957**, *22*, 1050–1053.
7. (a) Huff, B. E.; Staszak, M. A. A new method for the preparation of tetrazoles from nitriles using trimethylsilylazide/trimethylaluminum. *Tetrahedron. Lett.* **1993**, *34*, 8011–8014; (b) Wittenberger, S. J.; Donner, B. G. Dialkyltin oxide–mediated addition of trimethylsilyl azide to nitriles: A novel preparation of 5-substituted tetrazols. *J. Org. Chem.* **1993**, *58*, 4139–4141.
8. (a) Willfia, G. F.; Ronald, A. H.; Robert, L. An improved synthesis of 5-substituted tetrazoles. *J. Am. Chem. Soc.* **1958**, *80*, 3908–3911; (b) Eugene, L.; Takashi, E. Synthesis and properties of 5-(substituted) mercaptotetrazoles. *J. Org. Chem.* **1961**, *26*, 4472–4479; (c) Mathias, A.; Anders, H. Fast microwave-assisted preparation of aryl and vinyl nitriles and the corresponding tetrazoles from organo-halides. *J. Org. Chem.* **2000**, *65*, 7984–7989.
9. (a) Demko, Z. P.; Sharpless, K. B. An intramolecular [2 + 3] cycloaddition route to fused 5-heterosubstituted tetrazoles. *Org. Lett.* **2001**, *3*, 4091–4094; (b) Demko, Z. P.; Sharpless, K. B. Preparation of 5-substituted 1H-tetrazoles from nitriles in water. *J. Org. Chem.* **2001**, *66*, 7945–7950; (c) Demko, Z. P.; Sharpless, K. B. A click chemistry approach to tetrazoles by Huisgen 1,3-dipolar cycloaddition: Synthesis of 5-sulfonyl tetrazoles from azides and sulfonyl cyanides. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110–2113; (d) Demko, Z. P.; Sharpless, K. B. A click chemistry approach to tetrazoles by Huisgen 1,3-dipolar cycloaddition: Synthesis of 5-acyltetrazoles from azides and acyl cyanides. *Angew. Chem.,*

*Int. Ed.* **2002**, *41*, 2113–2116; (e) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. Why is tetrazole formation by addition of azide to organic nitriles catalyzed by zinc(II) salts? *J. Am. Chem. Soc.* **2003**, *125*, 9983–9987.

10. 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: Amsterdam, 1975.
11. Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. TBAF-catalyzed synthesis of 5-substituted 1*H*-tetrazoles under solventless conditions. *J. Org. Chem.* **2004**, *69*, 2896–2898.
12. (a) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. Novel synthesis of 5-substituted tetrazoles from nitriles. *Synthesis* **1998**, 910–914; (b) Tienan, J.; Fukuzou, S. K.; Yoshinori, Y. Copper-catalyzed synthesis of 5-substituted 1*H*-tetrazoles via the [3 + 2] cycloaddition of nitriles and trimethylsilyl azide. *Tetrahedron. Lett.* **2008**, *49*, 2824–2827.