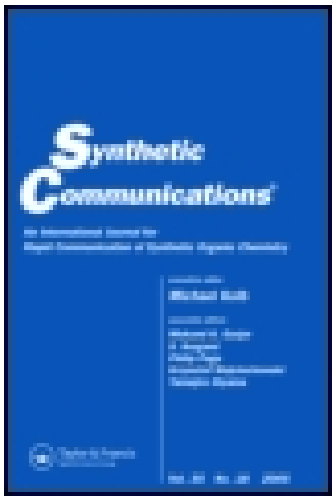

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Adiel Coca[a], Liana Feinn[a] & Joshua Dudley[a]

[a] Chemistry Department, Southern Connecticut State University, New Haven, Connecticut

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Microwave Synthesis of 5-Substituted 1*H*-Tetrazoles Catalyzed by Bismuth Chloride in Water

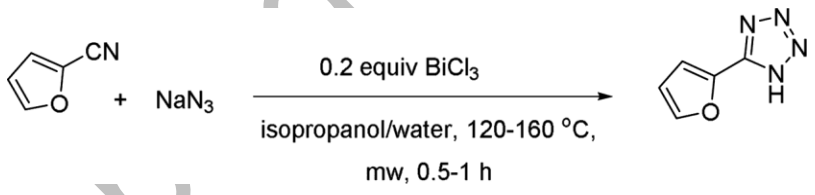
Adiel Coca[1], Liana Feinn[1], Joshua Dudley[1]

[1]Chemistry Department, Southern Connecticut State University, New Haven, Connecticut

Corresponding author E-mail: cocaa2@southernct.edu

Abstract

Bismuth chloride was used to catalyze the [2 + 3] cycloaddition between sodium azide with aryl nitriles, aliphatic nitriles, and vinyl nitriles. A number of 5-substituted 1*H*-tetrazoles were synthesized in water or isopropanol/water mixtures using microwave heating. High yields were obtained for these reactions when heated for one hour at 120-160 ^{o}C in a 3:1 isopropanol/water mixture. A few of the less reactive nitriles required longer reaction times for good yields.



KEYWORDS: [2 + 3] cycloaddition, bismuth chloride, 5-substituted 1*H*-tetrazoles, microwave, water

INTRODUCTION

Tetrazoles are interesting heterocycles with numerous applications. For example, tetrazoles are often used as bioisosteres for carboxylic acids due to similar acidity and planarity. The pK_a of tetrazole is approximately 4.90.[1] Tetrazoles offer the added

advantages that they are more metabolically stable, more lipophilic, and generally offer a more favorable pharmacokinetic profile than carboxylic acids. Thus, tetrazoles have been incorporated into several pharmaceuticals. For example, several approved angiotensin II receptor antagonists including avapro and diovan contain a tetrazole ring.[2] In addition, the tetrazole ring has also been incorporated into compounds that exhibited antiulcer,[3] antibacterial,[4] anticancer,[5] antiviral,[6] anti-inflammatory,[7] and antifungal[8] properties. Tetrazoles have also been employed in propellants, pyrotechnics and explosives. For example, 5-aminotetrazole can be used as a perchlorate replacement in flares.[9] Furthermore, tetrazoles have been incorporated in a proline-derived catalyst for asymmetric synthesis[10] and as ligands in coordination chemistry[11] as it can participate in at least seven coordination modes with metal ions. Tetrazoles have also been utilized as precursors to other five-membered ring heterocycles such as thiadiazoles using the Huisgen rearrangement.[12]

The synthesis of 5-substituted 1*H*-tetrazoles through a [2 + 3] cycloaddition of the azide anion and a nitrile was first reported in 1901.[13] This cycloaddition works best with aryl nitriles, especially when they are unhindered and contain an electron withdrawing group.[14,15] Although sodium azide is utilized most often, many other azide sources have been investigated including tin,[16] silicon,[17] and organoaluminum azides,[18]. Two reviews that cover recent developments in the synthesis of tetrazoles have been published.[19-20] Most examples in the literature to synthesize 5-substituted 1*H*-tetrazoles utilized an aprotic polar solvent such as dimethylformamide. For example, Sivaguru et al. used ceric ammonium nitrate supported on HY-zeolite to synthesize 5-substituted aryl

and benzylic 1*H*-tetrazoles in dimethylformamide with good yields after 2.5-9 h at 110 ^{o}C.[21] The post-transitional metal catalyst indium chloride has also been reported to catalyze this transformation in dimethylformamide.[22-23] The methodologies in these reports suffer from several disadvantages including long reaction times, high temperatures, and water-intolerant or expensive reagents. Recently, a few groups have used microwave heating to lower the reaction times.[24-25] Interestingly, Demko and Sharpless converted nitriles to tetrazoles in water and an isopropanol/water mixture using zinc salts as catalysts.[14] However, most substrates required 24 to 48 hours of heating at 100-170 ^{o}C and a large amount (0.5-1.0 equiv) of the zinc salt catalyst for good conversion. It has been suggested that the cycloaddition of nitriles and sodium azide occurs through either a two-step or concerted mechanism, where a Lewis acid catalyst helps active the nitrile for azide addition by coordinating the nitrile, but neither mechanism has been ruled out yet experimentally.[14,26] We recently reported the cycloaddition of various nitriles with sodium azide in water by using the rare-earth metal catalyst scandium triflate.[27] Here we report the preparation of 5-substituted 1*H*-tetrazoles in water and isopropanol/water mixtures by using 0.2 equiv of the post-transitional metal catalyst bismuth chloride ($BiCl_3$). The cycloaddition of various nitriles and sodium azide was accomplished in high yields with microwave irradiation for 30 minutes to 1 hour for most substrates.

RESULTS AND DISCUSSION

Preliminary experiments were performed using 4-nitrobenzonitrile (**1a**) in a multi-mode microwave reactor. Given the highly acidic and crystalline nature of tetrazoles, a basic

extraction followed by acidification afforded highly pure tetrazole products. Heating **1a** in a sealed Pyrex microwave vessel at 120 ^{o}C for 1 h with 0.2 equiv of $BiCl_3$ and with 2 equiv of NaN_3 led to a low yield (22%) of the tetrazole product when the reaction was done in water (Table 1). Performing the reaction in a 1:1 isopropanol/water mixture at 120 ^{o}C for 1 h increased the yield of the tetrazole to 44%. Using a 3:1 isopropanol/water mixture as the solvent and heating the reaction at 120 ^{o}C for 0.5 h, increased the yield further to 60%. Even better results were obtained when the 3:1 isopropanol/water mixture was heated at 120 ^{o}C for 1 h as 4-nitrobenzotetrazole (**2a**) was obtained in a 71% yield. At 120 ^{o}C, it was noticed that the nitrile was highly insoluble in water and even in the 1:1 isopropanol/water mixture. Increasing the reaction temperature to 140 ^{o}C (for 1 h) and using a 3:1 isopropanol/water mixture led to an 80% yield of **2a**. Switching the catalyst to $Bi(OTf)_3$ (0.2 equiv) and running the reaction in a 3:1 isoproponal/water mixture at 140 ^{o}C afforded only 61% of **2a** after 1 h. For this reason, $BiCl_3$ was used for the rest of this study. Heating the 4-nitrobenzonitrile reaction to 160 ^{o}C for 1 h increased the yield of the desired tetrazole further to 95% when the reaction was done in the 3:1 isopropanol/water mixture. Interestingly, running the reaction at 160 ^{o}C for 1 h in either water or a 1:1 isopropanol/water mixture led to a similar yield (89%) for **2a**. It appears that at the higher temperature, the water insolubility of 4-nitrobenzonitrile is less of an issue. At lower temperatures, a large amount of unreacted nitrile was seen especially when water or the 1:1 isopropanol/water mixture was used. Attempts with other nitriles such as 4-acetylbenzonitrile (**2b**) and 4-chlorobenzonitrile (**2c**) also led to low to moderate yields at lower temperatures. Similarly, low to modest yields were obtained for nitriles **2b** and **2c** when using water or 1:1 isopropanol/water as the solvent at 160 ^{o}C. In the case of nitrile

2b, using a 3:1 isopropanol/water mixture as the solvent and heating the reaction at 160 ^{o}C increased the yield considerably (78%). However, for nitrile **2c** there wasn't a significant increase in yield when using a 3:1 isopropanol/water mixture at 160 ^{o}C compared to a 1:1 isopropanol/water mixture.

Using these optimized conditions, several other tetrazoles were prepared. For example, 4-cyanobenzophenone (**1d**) and methyl 4-cyanobenzoate (**1e**) reacted to afford the corresponding tetrazoles in high yield (75 and 79%). Other *para*-substituted nitriles such as 4-bromobenzonitrile (**1f**) and the electron rich 4-methoxybenzonitrile (**1g**) afforded a relatively low yield of the 5-substituted tetrazole after 1 h (50% and 20%, respectively). Allowing these nitriles to react for 4 h at 160 ^{o}C led to an almost quantitative yield with **1f** and a 61% yield with **1g**. A 4 h reaction time is still a considerable improvement over most current methods used to prepare 5-substituted 1*H*-tetrazoles. By using 0.4 equiv of $BiCl_3$ and 4 equiv of NaN_3, 1,4-dicyanobenzene (**1h**) was also converted in high yield (82%) after 1 h at 160 ^{o}C.

Two *ortho*-substituted aryl nitriles were also investigated in this reaction as shown in Table 3. Among them, 2-nitrobenzonitrile (**1i**) did better as it was converted to the tetrazole in 74% yield whereas 2-chlorobenzonitrile (**1j**) afforded 37% of the tetrazole after 1h. The yield for the reaction with nitrile **1j** was increased to 56% by increasing the reaction time to 4 h. Previous reports have indicated that *para*-substituted nitriles are generally more reactive than the *ortho*-substituted nitriles.[14,15] Several heteroaryl nitriles were also investigated in the [2 + 3] cycloaddition with sodium azide. For example, 2-

furonitrile (**1m**) was converted to the tetrazole in almost quantitative yield at 150 ^{o}C. Pyrazinecarbonitrile (**1k**) and 3-thiophenecarbonitrile (**1l**) also afforded a high yield of the tetrazole whereas 1-isoquinolinecarbonitrile (**1n**) gave a moderate yield of the tetrazole. 1,3-Dicyanobenzene (**1o**) was converted in high yield with 0.4 equiv of $BiCl_3$ and 4 equiv of sodium azide.

Lastly, vinyl, benzylic, and aliphatic nitriles which are generally very unreactive in this reaction were investigated and the results can be seen in Table 4.[28] Fumaronitrile (**1p**) reacted well as it gave a very high yield when 4 equiv of sodium azide and 0.4 equiv of $BiCl_3$ were used. Cinnamonitrile (**1q**), on the other hand, performed poorly as only 38% of the tetrazole was obtained after 1 h. The yield for the reaction of nitrile **1q** was increased to 49% by increasing the reaction time to 4 h. Disappointedly, aliphatic nitriles exemplified by heptyl cyanide (**1r**) were not very reactive using $BiCl_3$ as a catalyst. Similarly, the benzylic nitrile mandelonitrile (**1s**) was also very unreactive.

CONCLUSION

In summary, bismuth chloride was found to be an effective catalyst in the [2 + 3] cycloaddition between nitriles and sodium azide in water and isopropanol/water mixtures. Under the optimized conditions several 5-substituted 1*H*-tetrazoles were prepared in good yields. With the use of microwave heating, the generally long reaction times for this cycloaddition was reduced to 1 h. The yields for some of the less reactive nitriles were improved by increasing the reaction time to 4 h. Even with the increased reaction time for

some nitriles, this methodology is still a significant improvement over alternative methods to make tetrazoles given that most reports require 16-48 h reaction times.

EXPERIMENTAL

Typical Experimental Methodology

Synthesis of 5-(furan-2-yl)-1*H*-tetrazole (**2m**). 2-Furonitrile **1m** (186 mg, 2 mmol), NaN_3 (260 mg, 4 mmol), $BiCl_3$ (126 mg, 0.4 mmol), and 8 mL of a 3:1 isopropanol/water mixture were added to a 30-mL Pyrex microwave vessel and capped. The microwave vessel was then placed in a Milestone Start Synth microwave reactor. The reaction was magnetically stirred and heated for 1 hour at 150 ^{o}C. The reaction was monitored by TLC using an ether/hexane mixture (typically 50/50) for development. The reaction mixture was then diluted with saturated aqueous sodium bicarbonate (20 mL) and washed with ethyl acetate (2 x 15 mL). The aqueous sodium bicarbonate layer was cooled with ice and acidified to a pH of 2 or less with concentrated hydrochloric acid, which was added drop-wise. The precipitate formed was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried with anhydrous sodium sulfate and decanted into a tared round bottom flask. The organic layer was concentrated under reduced pressure by rotary evaporation at 40 ºC and then under high vacuum. The tetrazole product was recrystallized from ethyl acetate and hexane. All reagents mentioned above were used unpurified.

NMR spectra were acquired on a spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C acquisitions. All ^{1}H NMR spectra were taken in DMSO-d_6 using DMSO as a standard at

2.52 ppm. All ^{13}C NMR spectra were taken in DMSO-d_6 using DMSO as a standard at 40.45 ppm. An IR spectrum was obtained using an FTIR spectrophotometer. A melting point was also obtained for the solid products. 5-(furan-2-yl)-1*H*-tetrazole (**2m**) is a light yellow solid. IR (KBr, thin film) ν_{max} (cm^{-1}): 3427 (br), 1645 (m); ^{1}H NMR (DMSO-d_6, δ): 11.94 (s, br, 1H), 8.05 (dd, *J* = 1.77, 0.78 Hz, 1H), 7.29 (dd, *J* = 3.51, 0.78 Hz, 1H), 6.79 (dd, *J* = 3.51, 1.80 Hz, 1H); ^{13}C NMR (DMSO-d_6, δ): 149.3, 147.0, 141.0, 113.9, 113.4; mp 199−200 ºC.

All tetrazoles made in this report are known and characterization data matched closely with literature values: **2a**,[14] **2b**,[29] **2c**,[30] **2d**,[31] **2e**,[32] **2f**,[23] **2g**,[14] **2h**,[33] **2i**,[28] **2j**,[18] **2k**,[14] **2l**,[34] **2m**,[18] **2n**,[35] **2o**,[33] **2p**,[14] **2q**,[14] **2r**,[14] **2s**[14].

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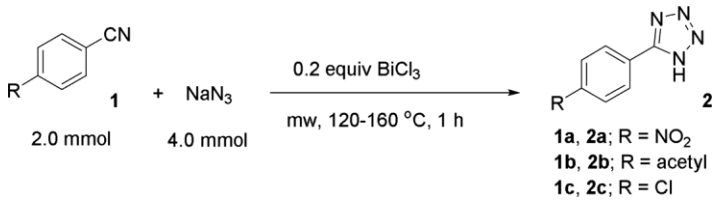
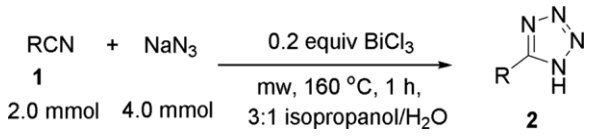
Table 1. Optimization Attempts.

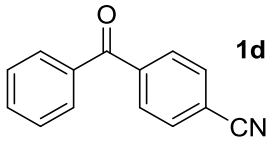
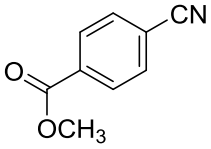
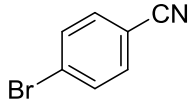
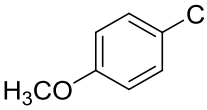
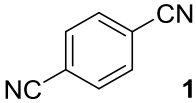


Nitrile	Solvent	Temperature (^{o}C)	% Yield
1a	H_2O	120	22
1a	1:1 isopropanol/H_2O	120	44
1[a]	3:1 isopropanol/H_2O	120	60[a]
1a	3:1 isopropanol/H_2O	120	71
1a	3:1 isopropanol/H_2O	140	80
1[a]	H_2O	160	89
1a	1:1 isopropanol/H_2O	160	89
1a	3:1 isopropanol/H_2O	160	95
1b	3:1 isopropanol/H_2O	120	19
1b	3:1 isopropanol/H_2O	140	58
1b	H_2O	160	40
1b	1:1 isopropanol/H_2O	160	57
1b	3:1 isopropanol/H_2O	160	78
1c	3:1 isopropanol/H_2O	120	14
1c	3:1 isopropanol/H_2O	140	40
1c	H_2O	160	17
1c	1:1 isopropanol/H_2O	160	60
1c	3:1 isopropanol/H_2O	160	61

[a] reaction time was 0.5 h.

Table 2. Reactions of *p*-Substituted Aryl Nitriles.

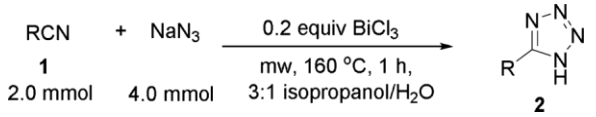


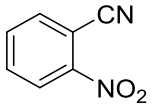
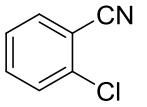
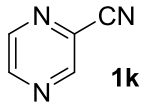
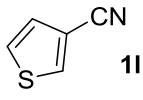
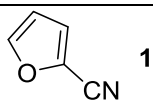
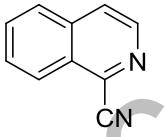
Substrate	% Yield
 **1d**	75
 **1e**	79
 **1f**[a]	98
 **1g**[a]	61
 **1h**[b]	82

[a] reaction time with nitriles **1f** and **1g** was 4 h.

[b] 8 mmol of NaN_3 and 0.4 equiv of $BiCl_3$ were used with nitrile **1h**.

Table 3. Reactions of non-*para*-Substituted Aryl Nitriles.



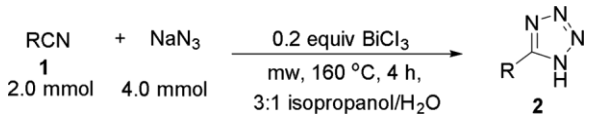
Substrate	% Yield
 **1i**	74
 **1j**[a]	56
 **1k**	78
 **1l**	84
 **1m**[b]	99
 **1n**	55
 **1o**[c]	77

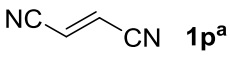
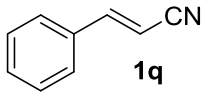
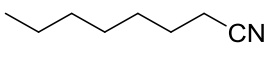
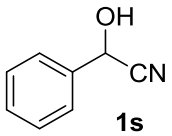
[a] reaction time with nitrile **1j** was 4 h.

[b] reaction temperature with nitrile **1m** was 150 °C.

[c] 8 mmol of NaN_3 and 0.4 equiv of $BiCl_3$ were used with nitrile **1o**.

Table 4. Reactions of Vinyl, Benzylic, and Aliphatic Nitriles.



Substrate	% Yield
 **1p**[a]	89
 **1q**	49
 **1r**	33
 **1s**	30

[a] 8 mmol of NaN_3 and 0.4 equiv of $BiCl_3$ were used with nitrile **1p** and reaction time was 1 h.