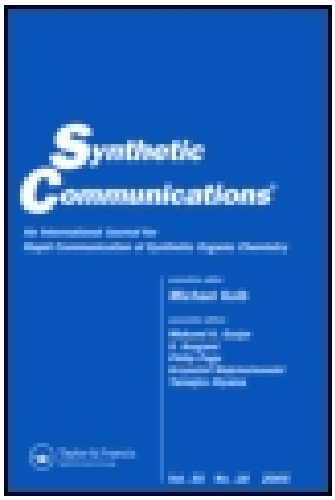

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Preparation of 5-Substituted 1*H*-Tetrazoles Catalyzed by Scandium Triflate in Water

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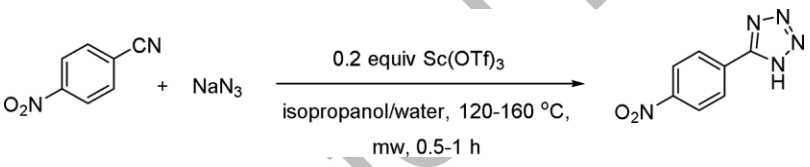
Abstract

Several 5-substituted 1*H*-tetrazoles were prepared in water or isopropanol/water mixtures using microwave heating. High yields were obtained for the [2 + 3] cycloaddition of sodium azide with aryl nitriles, aliphatic nitriles, and vinyl nitriles when catalyzed by scandium triflate. The reactions were typically heated for one hour at 160 °C in a 3:1 isopropanol/water mixture to obtain the best yields.



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

INTRODUCTION

Tetrazoles are a nitrogen rich heterocycle with a wide range of applications. Perhaps the most important application of tetrazoles is as a bioisostere for carboxylic acids since tetrazoles have a similar planarity and acidity to carboxylic acids.[1] Tetrazoles do offer

some advantages over carboxylic acids such as being more easily absorbed through biological membranes and being more metabolically stable than carboxylic acids. For these reasons, tetrazoles are incorporated in a number of pharmaceuticals including several approved angiotensin II receptor antagonists that are used to treat hypertension.[2] Tetrazoles are also used in explosives, propellant projectiles, and airbags in the automobile industry due to the high amount of energy stored within these rings.[3] In addition, tetrazoles are also an important precursor to other heterocyclic rings such as thiazoles, oxazolidones, and triazoles through the Huisgen rearrangement.[4,5] Moreover, tetrazoles have seen extensive use in coordination chemistry[6] and as catalysts in asymmetric synthesis.[7] Other applications of tetrazoles include being used as peptide chelating agents,[8] as lipophilic spacers,[9] as *cis*-peptide bond mimics,[10] in information recording systems,[11] as antifoggants in photography,[12] and in high-density energy materials.[13]

Typically 5-substituted 1*H*-tetrazoles are prepared through the [2 + 3] cycloaddition of an azide and a nitrile. Sodium azide (NaN_3) is usually used as the azide source, although silicon,[13] tin,[14] and organoaluminum azides[15] have also been explored. Most nitriles react well in this cycloaddition, although sterically unhindered and electron deficient aryl nitriles give the highest yields.[16,17] All of the currently available methods to synthesize tetrazoles through a [2 + 3] cycloaddition suffer from more than one of the following limitations: high temperatures, long reaction times, using toxic, expensive, or water sensitive reagents, and generation of hydrazoic acid, which is highly volatile, toxic, and explosive. In addition, most methods in the literature to make tetrazoles rely on using

aprotic organic solvents such as dimethylformamide (DMF). For example, recently 5-substituted 1*H*-tetrazoles were synthesized using microwave irradiation in DMF.[18] Demko and Sharpless demonstrated that the [2 + 3] cycloaddition of nitriles and sodium azide could be achieved in water or an isopropanol/water mixture using zinc salts such as $ZnBr_2$ as catalysts.[16] However, this methodology required 24 to 48 hours of heating at 100-170 ^oC for most substrates reported. Furthermore, a large amount (0.5-1.0 equiv) of the zinc salt catalyst was used. Here we report the synthesis of 5-substituted 1*H*-tetrazoles in high yields from various nitriles and sodium azide using 0.2 equiv of the rare-earth metal catalyst scandium triflate [$Sc(OTf)_3$]. The preparation of these tetrazoles was accomplished in water or an isopropanol/water mixture in 1 h using microwave irradiation. Although using water as a solvent in an organic reaction often poses some challenges, water (even as an isopropanol/water mixture) does provide practical and environmental advantages over organic solvents including being nontoxic, nonflammable, inexpensive, readily available, and easily disposed. Most organic chemists have hesitated from using water as a solvent due to the general insolubility of many organic compounds in water.

RESULTS AND DISCUSSION

Our studies were performed in a multi-mode microwave reactor in sealed Pyrex microwave vessels. Initial attempts to convert 4-nitrobenzonitrile (**1a**) at 120 ^oC in water using 0.2 equiv of $Sc(OTf)_3$ and with 2 equiv of NaN_3 led to a low yield (41%) of the tetrazole after 30 minutes of heating in the microwave reactor (Table 1). Increasing the temperature to 140 ^oC increased the yield to 60%. Given the insolubility of this nitrile in

water, an alcoholic co-solvent was tested. Running the same reaction with a 1:1 isopropanol/water mixture at 140 ^{o}C increased the yield but not significantly (66%). More satisfying was the fact that 4-nitrobenzonitrile in a 3:1 isopropanol/water mixture gave a 98% yield.

Since a small amount of unreacted nitrile was seen in the initial attempts in water and aqueous mixtures, the reaction temperature and reaction time were increased to 160 ^{o}C for 1 h. Using these conditions, the highly electron deficient 4-nitrobenzonitrile (**1a**) and 4-(trifluoromethyl)benzonitrile (**1b**) were quantitatively converted to the corresponding 5-substituted tetrazole (Table 2). Heating 4-chlorobenzonitrile (**1c**) with 2 equiv of NaN_3 and 0.2 equiv of $Sc(OTf)_3$ at 160 ^{o}C for 1 h afforded the corresponding tetrazole in 89% yield. Changing the catalyst from scandium triflate to ytterbium triflate hydrate decreased the yield for the 4-chlorobenzonitrile (**1c**) reaction to 80% under the same conditions. Thus, scandium triflate was used for the rest of the study.

Other *para*-substituted nitriles such as 4-methoxybenzonitrile (**1d**), 4-bromobenzonitrile (**1e**), 4-methylbenzonitrile (**1f**), and methyl 4-cyanobenzoate (**1g**) gave moderate to high yields (50-80%). 1,4-Diacyanobenzene (**1h**) was also converted in high yield (85%) when 0.4 equiv of $Sc(OTf)_3$ and 4 equiv of sodium azide were used. The results with the *para*-substituted aryl nitriles were very consistent with previous reports as the electron deficient nitriles were generally more reactive than the electron rich nitriles. [16,17]
Other aryl nitriles were also investigated in the [2 + 3] cycloaddition with sodium azide (Table 3). Most substrates tested gave moderate to high yields of the tetrazole with the exception of those that were sterically hindered. For example, *ortho*-substituted (2-

methoxyphenyl)acetonitrile (**1k**), 2-chlorobenzonitrile (**1m**), and 4'-methyl-2-cyanobiphenyl (**1n**) all failed to reach yields higher than 39%. Among the *ortho*-substituted aryl nitriles, 2-nitrobenzonitrile (**1l**) reacted well as it afforded a 76% yield of the tetrazole. Heterocyclic aryl nitriles such as 3-thiophenecarbonitrile (**1o**) and pyrazinecarbonitrile (**1q**) were converted in very high yields. Monosubstituted nitriles such as benzonitrile (**1i**), benzoyl cyanide (**1j**), and 1-cyanonaphthalene (**1p**) gave moderate yields of the tetrazole.

Vinyl and aliphatic nitriles were also reacted under the optimized conditions. Cinnamonitrile (**1r**) afforded a very low yield (39%) of the tetrazole but fumaronitrile (**1s**) was converted to the tetrazole in near quantitative yield with 0.4 equiv of $Sc(OTf)_3$ and 4 equiv of sodium azide. The two aliphatic nitriles tested, heptyl cyanide (**1t**) and cyclohexanecarbonitrile (**1u**), both gave identical yields (42%). Low yields for the aliphatic nitriles were expected based on previous reports.[16,17]

CONCLUSION

In conclusion, scandium triflate was determined to be a suitable catalyst for the [2 + 3] cycloaddition between nitriles and sodium azide in water and isopropanol/water mixtures in a multi-mode microwave reactor. Although the cycloaddition could be achieved after 30 minutes at 120 ^{o}C, the best results were obtained when the reaction was heated at 160 ^{o}C for 1 h. Several 5-substituted tetrazoles were synthesized under these conditions using only 0.2 equiv of $Sc(OTf)_3$. This methodology should provide a fast, reliable, and environmentally friendly route to other 5-substituted 1*H*-tetrazoles.

EXPERIMENTAL

Typical Experimental Methodology

Synthesis of 5-(4-chlorophenyl)-1*H*-tetrazole (**2c**). 4-chlorobenzonitrile **1c** (274 mg, 2 mmol), NaN_3 (260 mg, 4 mmol), $Sc(OTf)_3$ (197 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 160 ^{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 ^{0} C 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 40.5 ppm. An IR spectrum was obtained using an FTIR spectrophotometer. A melting point was also obtained for the solid products. 5-(4-chlorophenyl)-1*H*-tetrazole (**2c**) is a

white solid. IR (KBr, thin film) ν_{max} (cm^{-1}): 3385 (br), 1645 (m), 1634 (m); ^{1}H NMR (DMSO-d_6, δ): 11.60 (s, br, 1H), 8.07 (d, *J* = 8.28 Hz, 2H), 7.70 (d, *J* = 8.25 Hz, 2H); ^{13}C NMR (DMSO-d_6, δ): 155.8 (br), 136.9, 130.6, 129.7, 124.1; mp 250−251 °C.

All tetrazoles made in this report are known and characterization data matched closely with literature values: **2a**,[16] **2b**,[19] **2c**,[24] **2d**,[16] **2e**,[20] **2f**,[20] **2g**,[27] **2h**,[21] **2i**,[16] **2j**,[25] **2k**,[22] **2l**,[23] **2m**,[15] **2n**,[16] **2o**,[26] **2p**,[24] **2q**,[16] **2r**,[16] **2s**,[16] **2t**,[16] **2u**[18].

ACKNOWLEDGMENT

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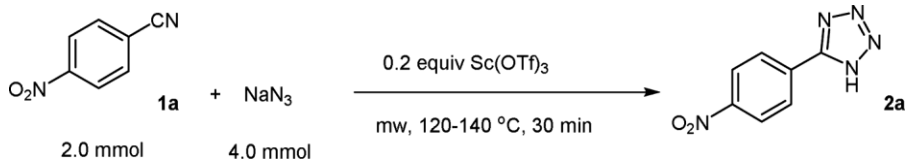
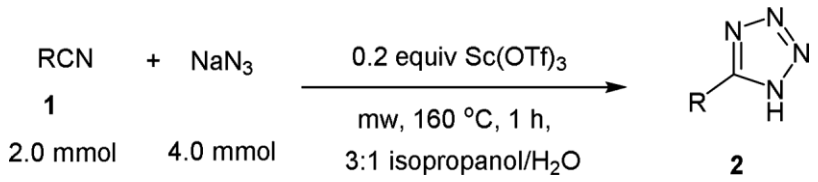
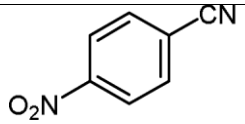
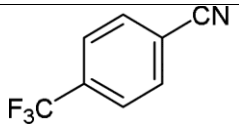
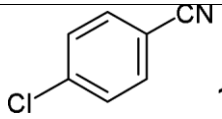
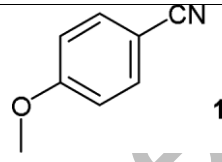
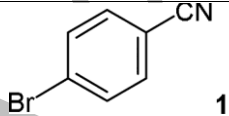
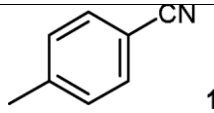
Table 1. Optimization attempts.

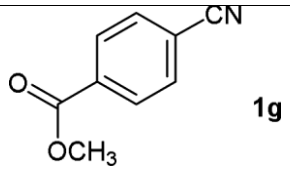
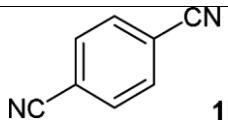


Solvent	Temperature (^{o}C)	% Yield
H_2O	120	41
H_2O	140	60
1:1 isopropanol/H_2O	140	66
3:1 isopropanol/H_2O	140	98

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

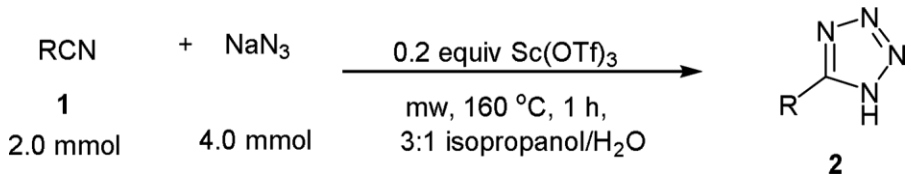


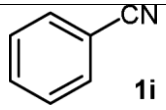
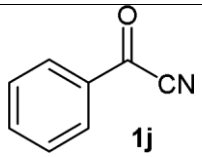
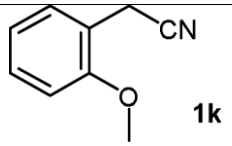
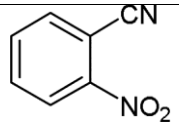
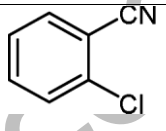
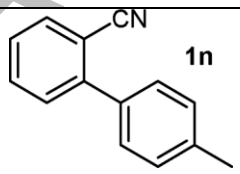
Substrate	Yield (%)
 **1a**	100
 **1b**	99
 **1c**	89
 **1d**	61
 **1e**	54
 **1f**	50

 **1g**	80
 **1h**[a]	85

[a]8 mmol of NaN_3 and 0.4 equiv of $Sc(OTf)_3 \cdot xH_2O$ were used with nitrile **1h**.

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



Substrate	Yield (%)
 **1i**	74
 **1j**	48
 **1k**	25
 **1l**	76
 **1m**	38
 **1n**	39

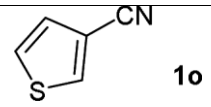
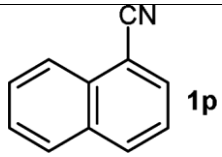
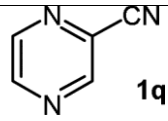
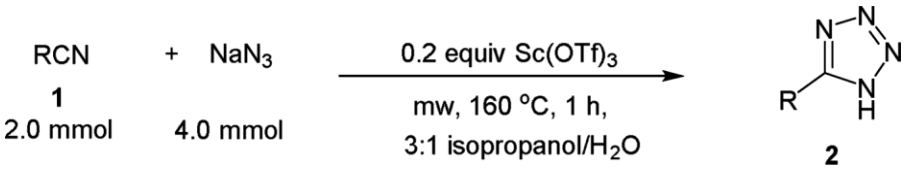
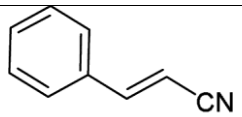
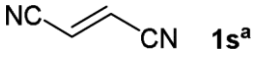
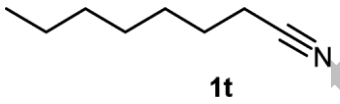
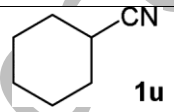
 **1o**	93
 **1p**	49
 **1q**	98

Table 4. Reactions of Vinyl and Aliphatic Nitriles.



Substrate	Yield (%)
 **1r**	39
 **1s**[a]	98
 **1t**	42
 **1u**	42

[a]8 mmol of NaN_3 and 0.4 equiv of $Sc(OTf)_3 \cdot xH_2O$ were used with nitrile **1s**.