Tin-Catalyzed Synthesis of 5-Substituted 1H-Tetrazoles from Nitriles: Homogeneous and Heterogeneous procedures

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Abstract. The preparation of 5-substituted 1H-tetrazoles was efficiently achieved by reaction of trimethylsilylazide with nitriles using a triorganotin alkoxide precatalyst. The reaction mechanism was first investigated using a homogeneous tributyltin derivative and was explored through experimental investigations and DFT calculations. A heterogeneous version was then developed using a polymer-supported organotin alkoxide and afforded an efficient method for the preparation of tetrazoles in high yields with an easy work-up and a residual tin concentration in the desired products compatible for pharmaceutical applications (less than 10 ppm).

Keywords: Azides; Stannanes; Tin; Cycloaddition; Solid-phase synthesis

Introduction

The tetrazole heterocycle has known an increasing interest in the last decades. Its use concerns many areas of chemistry such as medicinal chemistry,[1],[2] crop protection,[3] explosives,[4] coordination chemistry[5] or organocatalysis.[6] In medicinal chemistry, this interest is focused on the 5-substituted 1*H*-tetrazole unit which is considered as a carboxylic acid isostere for the design of active pharmaceutical ingredients.[7] The huge number of angiotensin II receptor blockers which contain a biphenyltetrazole framework is illustrative of this importance.[8] Therefore, the synthesis and functionalization of 5-substituted 1*H*-tetrazoles has been widely studied and numerous procedures have been reported and reviewed.[9] Due to the hazards encountered with the use of hydrazoic acid,[10] most of them involve the [3+2] cycloaddition of an azide anion to a nitrile in the presence of an acid. The cycloaddition presents a high activation barrier which prompted researchers to use additives or catalysts for milder experimental conditions. For instance, Brönsted or Lewis acids are efficient catalysts for this reaction, as well as metal salts which have been found to be efficient in stoichiometric or sub-stoichiometric quantities.[11]

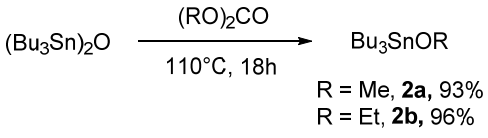
A literature survey reveals that one of the most efficient synthesis of 5-substituted 1*H*-tetrazoles involve an organotin azide generated *in situ* from trimethylsilyl azide and dibutyltin oxide,[12] or tributyltin chloride.[13] However the use of organotin reagents in synthetic chemistry is sometimes detrimental for the targeted applications due to the possible toxicity of organotin byproducts. To circumvent this issue, numerous procedures and methodologies have been developed to eliminate tin byproducts from the products and have been reviewed.[14] Most of these methodologies are based on partition methods starting from usual triorganotin reagents,[15] but some others involve highly polar organotin reagents[16] or media[17] as well as perfluorinated ones which highly improve the elimination of organotin by-products.[18]

The use of a catalytic amount of organotin reagents[19] or of monoorganotin reagents[20] have also been exploited, but the most efficient approaches to avoid contamination by organotin by-products remain the grafting of the organotin reagent on an appropriate substrate which can be a phosphonium salt,[21] an ionic liquid,[22] an inorganic matrix,[23] or an organic polymer.[14a-14d] While the above approaches have demonstrated their efficiency in numerous reactions, their use for the synthesis of 5-substituted 1*H*-tetrazoles has been overlooked. It is however worth noting that procedures for the synthesis of 5-substituted 1*H*-tetrazoles involving higher trialkylorganotin derivatives to facilitate the partition between polar products and unpolar tin byproducts have been reported.[24] In the same context, Curran *et al* have proposed an efficient procedure for the synthesis of 5-substituted 1*H*-tetrazoles using a perfluorotin azide and a fluorous/organic liquid-liquid extraction for the purification.[25]

Herein, we report the synthesis of 5-substituted 1*H*-tetrazoles from nitriles through a [3+2] cycloaddition catalyzed by tributyltin azide. This catalyst is generated in situ with tributyltin alkoxide and trimethylsilyl azide. The experimental and theoretical investigations are reported and discussed. The results related to the adaptation of this reaction to a heterogeneous phase reaction involving a polymer-supported catalyst,[26] allowing similar yields and avoiding the drawbacks of the removal of organotin residues are also described.

Results and Discussion

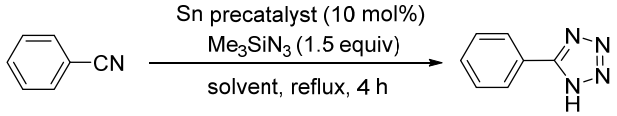
Scope and limitations of the reaction catalyzed by a tributyltin derivative. We set out to explore the synthesis of 5-substituted 1*H* tetrazoles **3** resulting from the addition of an organotin azide on a nitrile **1**. Our investigations started from contributions involving trimethylsilyl azide (Me_3SiN_3) and dibutyltin oxide considered in stoichiometric or in catalytic amount.[12] We focused on a dibutyltin oxide surrogate readily graftable on polymer. At this stage, we assumed that trialkyltin alkoxides could be valuable precursors of triorganotin azides and started our investigations by this consideration. Tributyltin methoxide **2a** and tributyltin ethoxide **2b** were prepared according to the literature, starting from bis(tributyltin) oxide and dimethyl or diethylcarbonate (scheme 1).[27]



Scheme 1. Preparation of tributyltin alkoxides **2a** and **2b**.

These tributyltin alkoxides were considered for the synthesis of 5-phenyl 1*H* tetrazole **3a** in different solvents starting from benzonitrile. The results obtained in this preliminary study using 10 mol% of **2a** or **2b** are reported in Table 1. When the reaction was carried out in toluene (entries 1 and 2), 5-phenyl 1*H*-tetrazole **3a** was obtained in low yields, regardless the tin catalyst although this solvent was extensively considered previously (entries 1 and 2).[12d] Similar results were observed when 1,2-dimethoxyethane was used (entries 3 and 4) and only moderate yields were obtained with 1,4-dioxane (entries 5 and 6). By considering polar solvents with high boiling points, high yields were obtained with DMF (entries 7 and 8), while NMP afforded only moderate yields (entries 9 and 10). Finally, yields were significantly improved using dibutylether (Bu_2O) as solvent (entries 11 and 12). Through these runs, we also observed that the presence of water, even in small quantities, had a dramatic negative effect on the yield as previously reported.[28] These results confirmed that trialkyltin alkoxides can act as precatalysts for the synthesis of 5-substituted 1*H*-tetrazoles. This screening also highlights that compound **2a** is more efficient than **2b**. Moreover, control experiments with dibutyltin oxide afforded lower yields in similar experimental conditions (entries 13 and 14). Similarly, when Bu_3SnCl was considered either with Me_3SiN_3 or with NaN_3, poor yields were obtained (entries 15 and 16). The latter results are in good agreement with a previous work reporting that a large excess (2.5 equiv) of both tributyltin chloride and sodium azide is required to obtain yields around 80%.[13b]

Table 1. Effect of solvent and catalyst on the formation of tetrazole **3a** from **1a.**



1a **3a**

Entry	Sn precatalyst	Solvent	T(°C)	Yield (%)
1	Bu_3SnOMe	toluene	110	15
2	Bu_3SnOEt	toluene	110	14
3	Bu_3SnOMe	DME	85	24
4	Bu_3SnOEt	DME	85	11
5	Bu_3SnOMe	1,4-dioxane	100	44
6	Bu_3SnOEt	1,4-dioxane	100	42
7	**Bu_3SnOMe**	**DMF**	**150**	**93**
8	Bu_3SnOEt	DMF	150	57
9	Bu_3SnOMe	NMP	150	53
10	Bu_3SnOEt	NMP	150	47
11	**Bu_3SnOMe**	**Bu_2O**	**140**	**99**
12	**Bu_3SnOEt**	**Bu_2O**	**140**	**85**
13	$(Bu_2SnO)_n$	DMF	150	45
14	$(Bu_2SnO)_n$	Bu_2O	140	73
15	Bu_3SnCl	Bu_2O	140	26
16	Bu_3SnCl [a]	Bu_2O	140	18

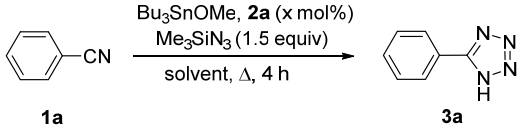
[a] $TMSN_3$ was replaced by NaN_3 (1.5 equiv).

Then, precatalyst loading tests were performed with 2, 5 and 10 mol% of **2a** in DMF or in Bu_2O and it appeared that 10 mol% of catalyst was necessary to obtain yields over 90% after 4 h (Table 2). When reducing the amount of **2a** to 5 and 2 mol%, yields in **3a** significantly decreased while control experiments confirmed that no reaction

occurred in the absence of **2a**. Furthermore, when Me_3SiN_3 was replaced by NaN_3, the yield was found to be low (9%, entry 9).

At this stage, the scope of the reaction for substituted benzonitriles was investigated using **2a** as precatalyst in DMF at 150 °C and in Bu_2O at 140 °C. The results reported in Table 3, revealed that a large variety of substituents were found to be compatible with the procedure. Both electron-donating and electron-withdrawing groups on the aryl moiety afforded efficiently tetrazole products **3a**-**3p**.

Table 2. Effect of precatalyst loading and solvent on the conversion of benzonitrile into tetrazole **3a**.



1a **3a**

Entry	Solvent	x (mol%)	T(°C)	Yield (%)
1	DMF	0	150	0
2	DMF	2	150	48
3	DMF	5	150	51
4	**DMF**	**10**	**150**	**93**
5	Bu_2O	0	140	0
6	Bu_2O	2	140	32
7	Bu_2O	5	140	76
8	**Bu_2O**	**10**	**140**	**99**
9	Bu_2O	10	140	9[a]

[a] Me_3SiN_3 was replaced by NaN_3 (1.5 equiv)

Aromatic nitriles bearing electron-donating groups like *p*-Me, *p*-OMe, *p*-NEt_2 afforded good yields of products **3b, 3c** or **3d**. Similarly, aromatic nitriles bearing electron withdrawing groups (*m*-OMe, *p*-NO_2, *m*-Cl, *p*-Cl, *m*-CF_3) afforded excellent yields in products **3f, 3g**, **3h**, **3i** or **3j**. In addition, 4-hydroxybenzonitrile gave the corresponding tetrazole **3k** in good yield, while methyl 4-cyanobenzoate afforded 4-(1H-tetrazol-5-yl)benzoic acid **3l** due to the hydrolysis of the ester function during the workup procedure. On the other hand, moderate to low yields were obtained with *ortho* substituted aromatic nitriles (tetrazoles **3m**, **3n**, **3o**), indicating that the reaction is sensitive to the steric hindrance near the nitrile group. However, 1-naphtonitrile where the effective hindrance on the α-position is lower and the activation of the nitrile higher when compared to *ortho* biphenyl nitrile, afforded high yield (**3p**). Finally, we investigated the reactivity of aliphatic nitriles and found that the procedure was also efficient for these substrates. Phenylacetonitrile, valeronitrile and nonanenitrile furnished the desired tetrazoles **3q-s** in good to moderate yields in the same reaction conditions, underlining the efficiency of the methodology since these substrates are poorly reactive in this type of reaction with other methods.[11e]

Experimental investigations of the reaction mechanism. At this stage, further investigations were conducted in order to collect insights on the reaction mechanism. The reactive species supposed to be formed in this reaction is tributyltin azide (Bu_3SnN_3). Therefore, its synthesis was carried out using a described procedure starting from tributyltin halide and NaN_3 (Table 4).[29] Due to the low solubility of NaN_3 in organic solvents, different experimental conditions were considered for this reaction. A careful monitoring of the reaction using ^{119}Sn NMR revealed a complete conversion of Bu_3SnX to Bu_3SnN_3 after 18 h at room temperature. When NaN_3 was replaced by Me_3SiN_3, the reaction was found to proceed faster due to the higher miscibility of Me_3SiN_3 with Bu_3SnCl, and

conversion to Bu_3SnN_3 was observed at room temperature in a few minutes. After distillation, Bu_3SnN_3 was obtained in 95% yield and characterized by FT-IR and ^{119}Sn NMR. Interestingly, the ^{119}Sn chemical shift was found to be strongly solvent dependent as reported in table 4. These differences in chemical shifts can be explained by the modification of the tin hybridization from sp^3 to sp^3d due to intermolecular interactions between the tin atom and a solvent heteroatom or a nitrogen atom of a second molecule of Bu_3SnN_3.[30]

Table 3. Synthesis of 5-substituted 1*H*-tetrazoles promoted by Bu_3SnOMe, **2a**.

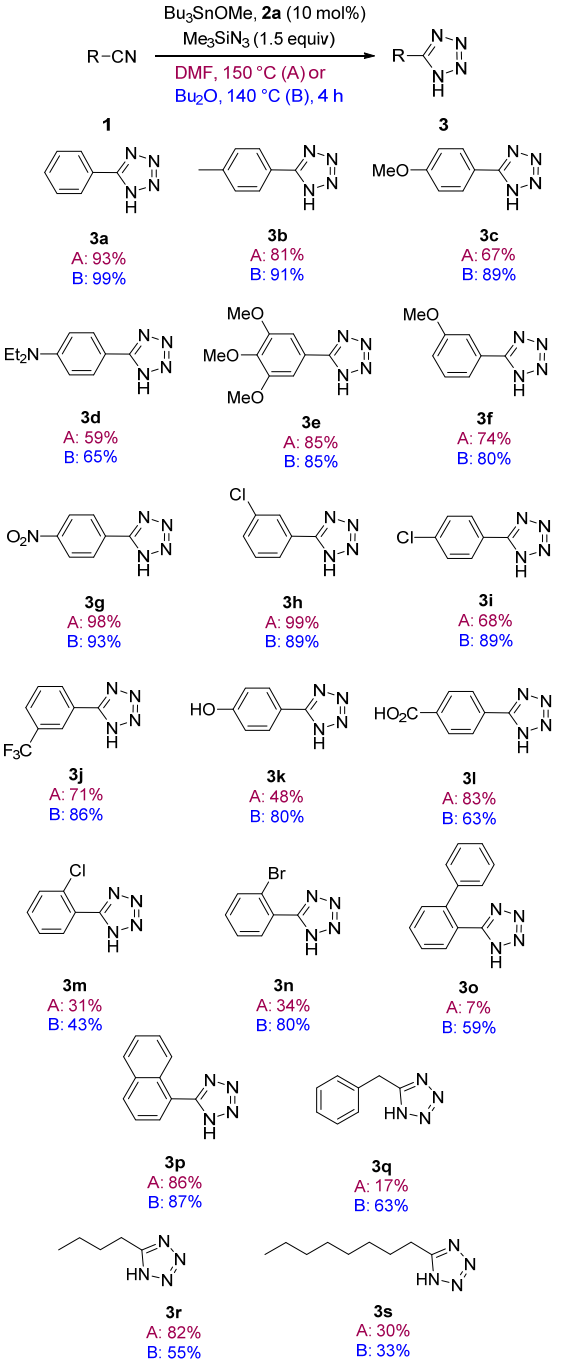
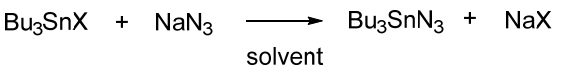


Table 4. Solvent dependence of ^{119}Sn NMR chemical shift for Bu_3SnN_3.

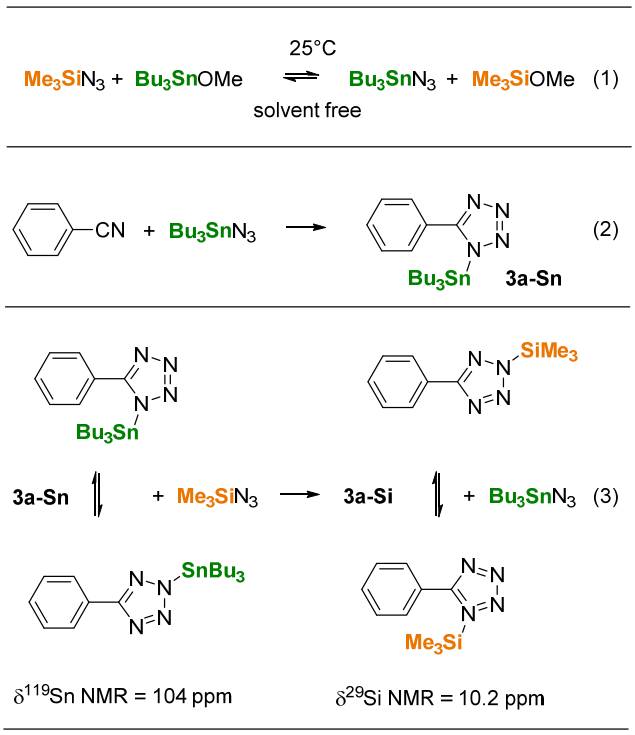


Entry	Bu_3SnX	Solvent	δ^{119}Sn (Bu_3SnN_3) (ppm)[a]
1	Bu_3SnI	without	76
2	Bu_3SnI	DMF-d7	-51
3	Bu_3SnI	THF-d8	66
4	Bu_3SnCl	without	63
5	Bu_3SnCl	C_6D_6	103
6	Bu_3SnCl	$CDCl_3$	111

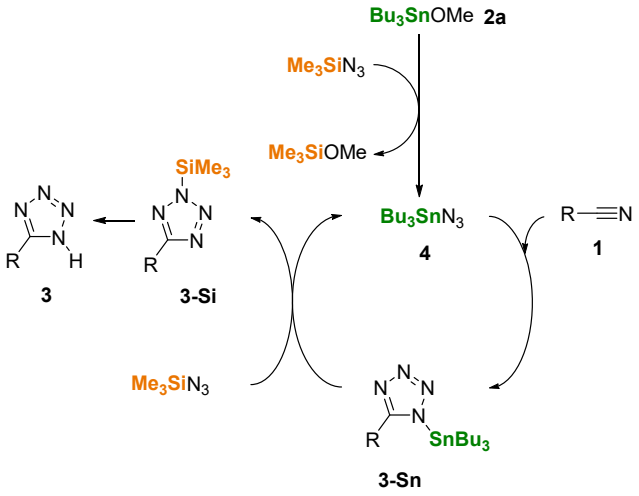
[a] Me_4Sn (δ = 0 ppm) was used as internal standard for chemical shift measurement.

When the reaction between Bu_3SnOMe and Me_3SiN_3 was carried out without any solvent at 25°C, a NMR monitoring by ^{119}Sn NMR and ^{29}Si NMR conducted at room temperature reveals the occurrence of a partial exchange after 1 hour (Scheme 2, eq 1). Indeed, two signals were observed on both spectra, corresponding to Bu_3SnOMe (δ = 113 ppm) and Bu_3SnN_3 (δ = 63 ppm) on ^{119}Sn NMR spectrum, and to Me_3SiN_3 (δ = 16.6 ppm) and Me_3SiOMe (δ = 19.5 ppm) on ^{29}Si NMR spectrum. In addition the FT-IR spectrum clearly exhibits the characteristic band at 2065 cm^{-1} ascribed to the vibration $\nu_{as}N_3$ in Bu_3SnN_3.[31] Furthermore, the reaction between benzonitrile and tributyltin azide does not occur at room temperature and requires an appropriate heating (4 h at 140 °C) to afford *N*-tributylstannyl 5-phenyl 1*H*-tetrazoles **3a-Sn** (Scheme 2, eq 2).[12a],[32] After 4 h at 140 °C, the solvent-free reaction afforded quantitatively **3a-Sn**, which was isolated and characterized in spite of its sensitivity to hydrolysis. Note that well defined signals were observed in ^{13}C NMR spectrum, while broader signals were observed in ^{1}H and ^{119}Sn NMR spectra, a result which is in agreement with the possible intermolecular associations and metallotropy.[32] All attempts to isolate the silylated tetrazole (intermediates **3a-Si**) obtained by reaction between **3a-Sn** and Me_3SiN_3 were unsuccessful (Scheme 2, eq 3). However, when the reaction was performed in a NMR tube under inert atmosphere, the ^{29}Si NMR spectrum exhibits a signal at 10.2 ppm, different from the chemical shifts of Me_3SiN_3 (16.6 ppm) and Me_3SiOMe (19.5 ppm)[33] which could be assigned to intermediates **3a-Si**.

Based on these results and taking into account previous proposed mechanism,[12d] we considered the catalytic cycle described in scheme 3 as a plausible one. First the precatalyst **2a** reacts with trimethylsilyl azide to afford tributylstannyl azide which is the active species of the reaction. This reaction proceeds at room temperature and therefore cannot be the limiting step.



Scheme 2. Tributyltin azide: its generation and its reactivity with benzonitrile.



Scheme 3. Proposed mechanism for the synthesis of 5-substituted 1*H*-tetrazoles promoted by Bu_3SnOMe.

The reaction between tributyltin azide and nitrile exhibits a higher energetic barrier to lead to adducts **3a-Sn**. The latter reacts with another molecule of trimethylsilyl azide to give intermediates **3a-Si** with concomitant regeneration of Bu_3SnN_3 and finally a protonolysis of **3a-Si** affords the 5-phenyl 1*H*-tetrazole **3a**.

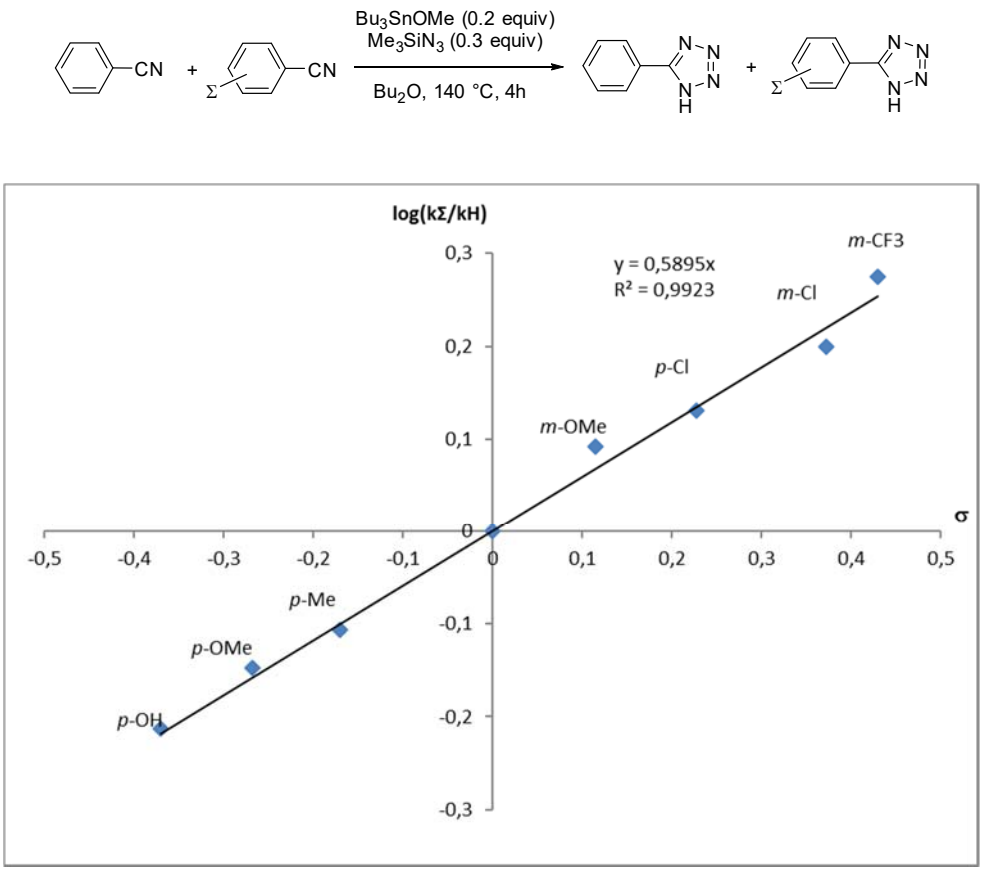
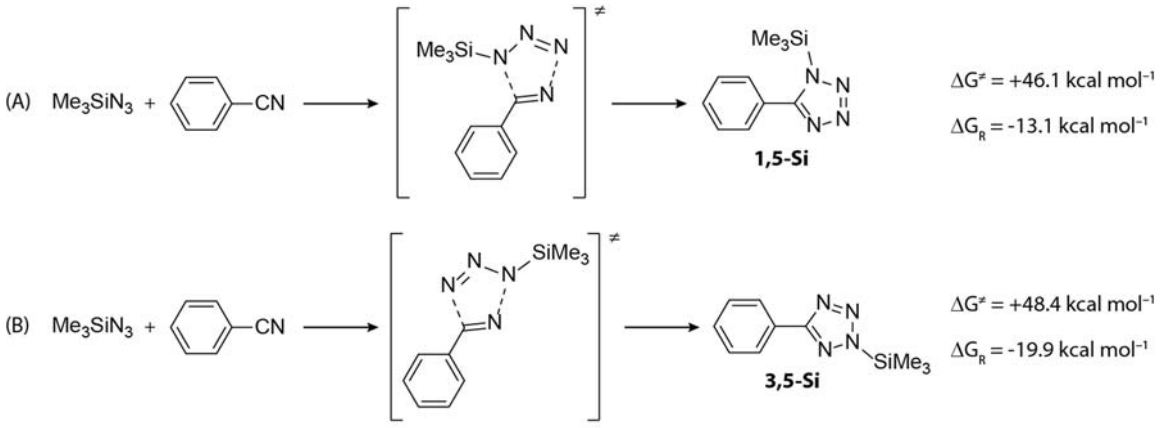


Figure 1. Hammett plot for reactivity of substituted benzonitriles with in situ generated tributyltin azide.

At this stage, it remains to clarify the intimate mechanism of the rate determining step of the reaction in order to establish its synchronous or non-synchronous character. For this purpose, we have conducted additional experimental investigations. We have carried out competitive experiments between benzonitrile and *meta*- or *para*- substituted benzonitriles in order to establish a Hammett relationship based on the relative kinetics of these reactions. These experiments have been carried out according to the Doering-Henderson approximation (reactant/substrate ratio = 1/5)[34] to ensure accurate measurements in line with kinetics for Hammett relationship.[35] As suggested from yields given in Table 3, benzonitriles substituted by strong electron-withdrawing groups exhibited a higher reactivity when compared to those substituted by electron releasing ones. As shown in Figure 1, a Hammett ρ.σ relationship was obtained with a calculated ρ-value of +0.58. This positive ρ-value is indicative of a slight negative charge at the benzylic carbon in the transition state, a result in agreement with a nucleophilic attack of the azide on the carbon of the nitrile group probably combined with an electrophilic assistance of tin on the nitrogen atom of the nitrile.

DFT investigations of the reaction mechanism. Further investigations have been performed by means of quantum mechanical calculations at the BMK/cc-pVDZ level of theory. The presented free energies are corrected from solvent effects and are computed for the 140 °C and 1 mol.L^{-1} standard state. At first, we considered the mechanism of the reaction between Me_3SiN_3 and benzonitrile in the absence of catalyst. In agreement with the pioneering computational work of Noodleman and Sharpless,[36] dealing with the elucidation of the mechanisms

of tetrazole formation by addition of azide to nitriles, two different pathways have been characterized which correspond to the formation of either 1,5 or 3,5-regioisomers **3a-Si** (scheme 4). Both (A) and (B) reaction pathways exhibit an energy barrier, corresponding to a concerted [3+2] cycloaddition. The respective values, 46.1 kcal mol^{-1} and 48.4 kcal mol^{-1} with respect to the reactants, are calculated in good agreement with previous DFT values obtained by Kappe *et al.*[37] for the cycloaddition of Me_3SiN_3 with acetonitrile. These high energy barriers are consistent with the absence of reaction at 140 °C between Me_3SiN_3 and benzonitrile although the reaction is predicted exergonic ($\Delta G_R < 0$).



Scheme 4. Evaluation of the activation energy for uncatalyzed cycloaddition of Me_3SiN_3 to benzonitrile (computed at the BMK/cc-pVDZ level of theory).

Then, we studied the influence of the triorganotin alkoxide on the reaction between Me_3SiN_3 and benzonitrile. The catalytic cycle described in scheme 3 was notably investigated. Computational considerations prompted us to use Me_3SnN_3 as model compound in order to mimic Bu_3SnN_3. In principle, Me_3SnN_3 can react with benzonitrile according to the (A) and (B) mechanisms depicted for the direct reaction with Me_3SiN_3. Indeed, a possible reaction pathway involving a synchronous cycloaddition, as in (A), and leading to a 1,5-disubstituted **3-Sn** species was evidenced (Figure 2). However, the predicted energy barrier, 45.5 kcal mol^{-1} with respect to the reactants, is close to that calculated for the uncatalyzed reaction, which suggests that this process cannot occur in our experimental conditions. In agreement with the work of Kappe *et al.* on tin-catalyzed addition of Me_3SiN_3 to acetonitrile,[37] we found that the (B) reaction pathway is markedly modified (Figure 2). A stepwise mechanism emerges, beginning with the approach of the benzonitrile nitrogen on the acidic tin atom of Me_3SnN_3, while the nitrile carbon is activated for the addition of the azide. This process leads to the open-chain reaction intermediate **RI B1**, through the transition state **TS B1** computed 34.9 $kcal.mol^{-1}$ above the reactants., which is the rate-determining step of the reaction. The next steps are part of the ring-closing process. The latter involves two smaller energy barriers (25.6 and 30.3 kcal mol^{-1} with respect to the reactants), a further open-chain reaction intermediate (**RI B2**), and results in the formation of a 1,5-disubstituted **3-Sn** species (with a reaction free energy of -14.6 kcal mol^{-1}). According to eq. 3 of scheme 2, the latter would react with Me_3SiN_3 to afford the **3a-Si** species, while recovering the catalyst. Note that such efficient recovery process of the catalyst was already disclosed for organotin-catalyzed cycloaddition between Me_3SiN_3 and acetonitrile.[37]

Thus, it exists a stepwise mechanism that (i) lowers significantly the activation free energy, by 11.2 kcal mol^{-1} with respect to the uncatalyzed reaction, and (ii) could explain the observed high yield for the reaction between Me_3SiN_3 and benzonitrile when Bu_3SnN_3 was in situ generated. Additional clues are provided through the comparison between observed trends for substituted benzonitriles and those predicted by DFT calculations. We assumed that the first step of the (B) pathway control the reaction kinetic. Experimentally, the reaction with the *meta*-chlorobenzonitrile proceeds 1.6 faster than the one with unsubstituted benzonitrile, and the reaction with the *para*-hydroxybenzonitrile is 1.6 slower than the one with unsubstituted benzonitrile. We have computed the energy barriers corresponding to the activation of the nitrile in the *meta*-chlorobenzonitrile (34.2 kcal mol^{-1}) and in the *para*-hydroxybenzonitrile (35.5 kcal mol^{-1}). According to the transition state theory and the resulting Eyring's equation,[38] these values lead to a rate constant for the *meta*-chlorobenzonitrile 2.3 larger than for the unsubstituted benzonitrile, and a rate constant for the *para*-hydroxybenzonitrile 2.1 smaller than for the unsubstituted benzonitrile. There is clearly a good agreement with experiments, which supports the proposed mechanism for the tin-catalyzed formation of 5-substituted 1*H*-tetrazoles.

Reaction catalyzed by a polymer-supported tin derivative. Considering our previous works related to polymer-supported tin reagents,[39] we then embarked in the adaptation of this reaction to the solid phase using organotin reagents grafted on an insoluble polystyrene matrix. Indeed these supported organotin reagents brings important advantages concerning the removal of tin byproducts from the reaction products which can be achieved by a simple filtration allowing less than 10 ppm as total tin in the desired products. Due to the numerous applications of the tetrazole moiety, such strategy presents a major interest to obtain compounds of high purity. To the best of our knowledge, there is only a few cases where the tin mediated tetrazole synthesis has been developed with the aim to limit the amount of residual tin in the reaction product.

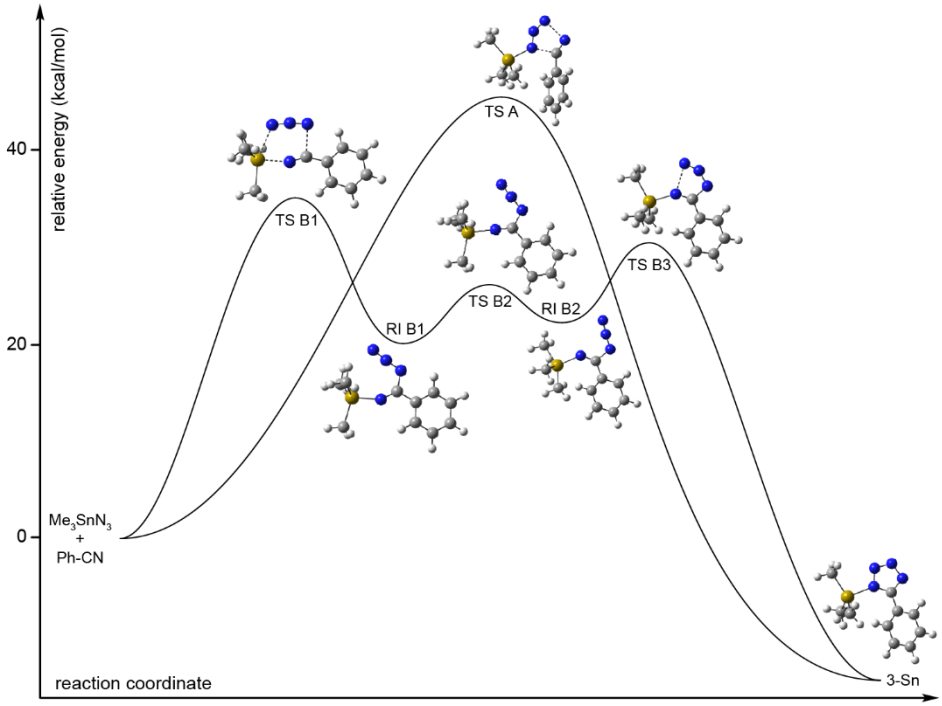
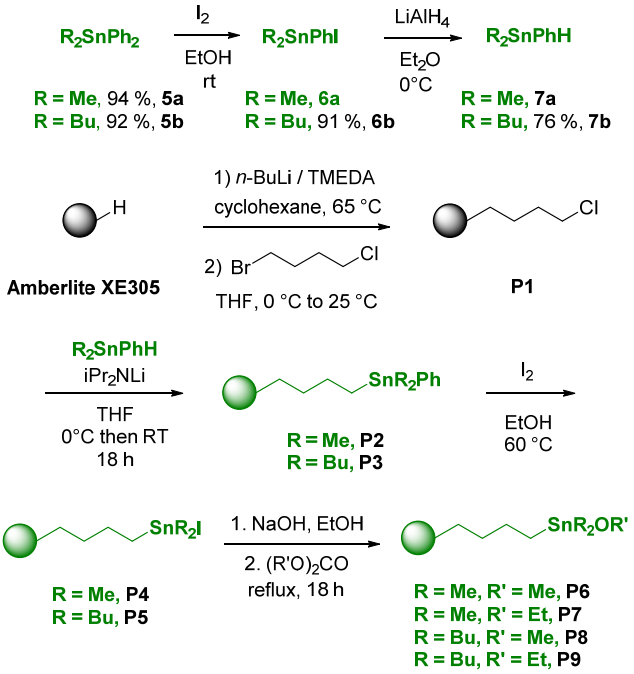


Figure 2. Free energy surface for the reaction between Me_3SnN_3 and benzonitrile (computed at the BMK/cc-pVDZ level of theory, geometries and individual energies are provided in the Supporting Information). Atom colour code: yellow for Sn, blue for N, gray for C and white for H.

These processes concerns the use of a trioctyltin reagent to improve the partition between polar and unpolar compounds,[24] or the use of a perfluoroalkyltin azide and a fluorous/organic liquid/liquid extraction.[25] Otherwise, a crosslinked polystyrene-supported azidostannane has been recently reported with its use for the synthesis of aryl azides.[40]

According to our mechanistic studies, we required a polymer which was not temperature sensitive like Amberlite XE305, a commercially available macroporous polystyrene reticulated with 10-12% of divinylbenzene. This polymer is resistant to abrasive effect induced by stirring and allow good loading (~1.5 mmol.g^{-1}). In addition, a tetramethylene spacer was required to minimize the steric hindrance both for trimethylsilyl azide / triorganotin alkoxide exchange and for addition of the azide on the nitrile. We prepared four different polymer-supported tin precatalysts **P6-P9** having different steric hindrance around the tin atom. Briefly, the reaction sequence involves the lithiation of Amberlite XE305 followed by its reaction with 1-bromo-4-chlorobutane leading to polymer **P1** (Scheme 5). A subsequent stannylation reaction with dialkylphenylstannyl lithium, afforded the stannylated polymers **P2**[41] and **P3** whose iododearylation with iodine in ethanol furnished polymers **P4** and **P5**. Finally, a reaction with sodium hydroxide in methanol followed by reflux in dimethyl or diethylcarbonate during 18 hours led to supported organotin alkoxides **P6-P9**. The tin loading of **P2** and **P3** were found to be 1.2 mmol.g^{-1} and 1.33 mmol.g^{-1} respectively from tin ICP analyses and ^{119}Sn MAS NMR analyses of polymers **P2-P9** pointed out an apparent quantitative conversion in every subsequent steps of these heterogeneous reactions.

Precatalysts **P6-P9** were then involved in the synthesis of 5-substituted 1*H*-tetrazoles for comparison with the results obtained with **2a** and **2b**. We first evaluated the four polymer-grafted alkoxystannanes for the synthesis of **3a** (Table 5).

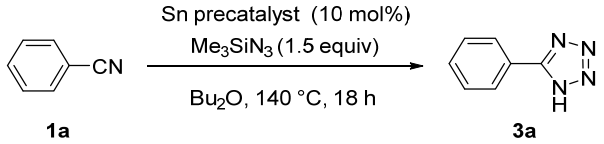


Scheme 5. Preparation of polymer-supported triorganotin alkoxides.

In the typical procedure, benzonitrile was reacted with Me_3SiN_3 in Bu_2O in the presence of 10 mol% of polymer-supported organotin precatalyst at 140 °C. Initial attempts with a reaction time of 4 hours only afforded moderate

yields. Further studies reveal that good yields could be obtained by carrying out the reaction under reflux during 18 hours. This difference can be explained by the heterogeneous nature of the reaction involving catalysts **P6-P9**, which usually lowers reaction kinetics.[39f] The reaction work-up used for these reactions was similar to those applied for homogeneous conditions but was preceded by a filtration to remove the insoluble supported organotin byproducts. By screening the four different catalysts, we observed that the less bulky was the alkoxide group of the precatalyst (**P6** and **P8**), the higher was the reaction yield. We also noted that the replacement of two butyl groups linked to the tin atom by two methyl groups (**P6** and **P7**) influenced more significantly the yield than the exchange of the ethoxy group by a methoxy group, a result in good agreement with the reaction mechanism which requires minimization of the steric hindrance to facilitates both the Si-N_3/Sn-OR exchange affording the effective active species and the addition reaction of the tin azide on the nitrile.

Table 5. Screening of the polymer supported organotin alkoxides for the synthesis of **3a**.

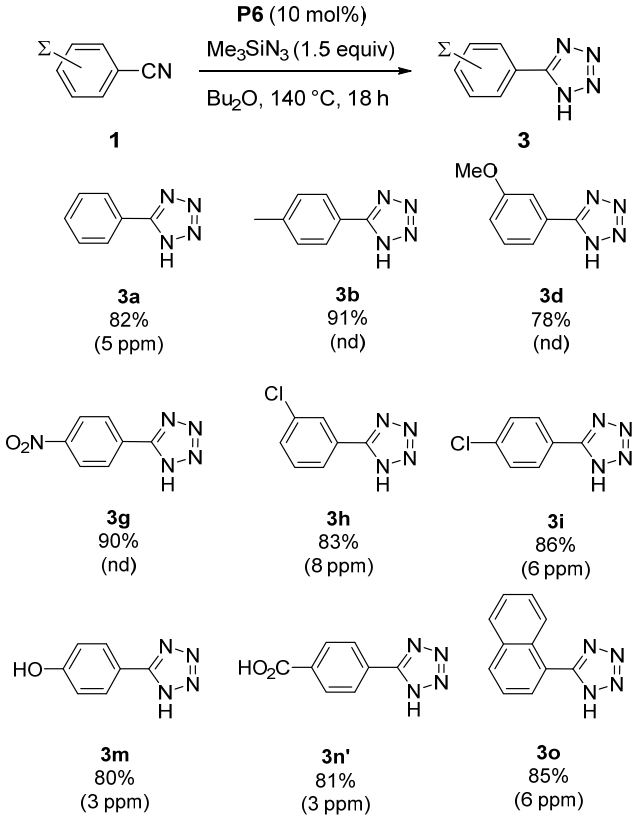


1a **3a**

Entry	Sn precatalyst		Yield (%)
1	$SnMe_2OMe$	**P6**	82
2	$SnMe_2OEt$	**P7**	75
3	$SnBu_2OMe$	**P8**	70
4	$SnBu_2OEt$	**P9**	68

We next extended the reaction study involving precatalyst **P6**, and for this purpose a selection of both electron poor and electron rich aromatic nitriles was considered. The reaction procedure was similar to that applied to benzonitrile. Remarkably, very good yields were obtained indicating that these heterogeneous conditions do not affect significantly the catalytic system when the reaction time is prolonged from 4 hours to 18 hours (Table 6). In addition, after work-up and isolation of the reaction product, several analysis by ICP-MS were carried out and exhibited a low residual tin concentration (under 10 ppm) to be compared with a concentration of 1000 ppm obtained with catalyst **2a** or **2b**. This results points out the efficiency of this methodology which is compatible for the synthesis of pharmaceutical substances.[42]

Table 6. Synthesis of 5-substituted 1*H*-tetrazoles promoted by polymer supported organotin alkoxides.[a], [b]



[a] Isolated yields; [b] concentration in tin residues in the reaction product measured as total tin by ICP-MS; nd = not determined

Conclusion

Triorganotin alkoxides were found to be efficient precatalysts for the synthesis of 5-substituted 1*H*-tetrazoles starting from nitriles and Me_3SiN_3 through the in situ generation of triorganotin azide. These precatalysts were found to be more efficient than dibutyltin oxide or tributyltin chloride often used for this reaction. The reaction scope is quite large, includes aryl and also alkyl nitriles and tolerates a wide variety of functional groups. The reaction mechanism is believed to proceed by a nucleophilic attack of the azide on the nitrile with a concomitant assistance of the tin on the nitrile nitrogen as suggested by Hammett relationship and quantum mechanical calculations. The mechanistic study underlines the importance of the polarization of the tin azide bond and of the steric hindrance both for trimethylsilyl azide / triorganotin alkoxide exchange and for addition of the azide on the nitrile. Finally, a heterogeneous version of the reaction has been developed and four polymer-supported organotin alkoxides have been prepared and evaluated as precatalysts for the reaction. The higher yields were obtained with the less hindered organotin alkoxide bearing a $(CH_2)_4$-$SnMe_2OMe$ appendage. The 5-substituted 1*H*-tetrazoles were prepared in high yields using this precatalyst and ICP-MS analyses confirmed the high efficiency of this procedure to avoid the presence of residual tin in the reaction products.

Experimental Section

General procedure for the synthesis of 5-substituted-1H-tetrazoles 3 promoted by 2a. In a sealable tube, a solution of nitrile (2.5 mmol), trimethylsilyl azide (432 mg, 497 µL, 3.75 mmol), precatalyst **2a** (80.3 mg, 0.25 mmol) in dry dibutyl ether (5 mL) was prepared and stirred for 4h at 140°C. The resulting mixture was cooled to 0°C and quenched with 5 mL of NaOH (1N) and 15 mL of petroleum ether. The aqueous phase of the filtrate solution is separated from the organic one and acidified to pH = 1 at 0°C in order to obtain the tetrazole as a solid. After filtration, the solid was dried under vacuum. The procedure was similar when catalyst **2b** was used, or when DMF was the solvent (reaction temperature = 150°C in this case).

General procedure for 5-substituted-1H-tetrazoles synthesis 3 promoted by P6-P9. A sealable tube was charged with polymer **P6** or **P7** (210 mg, tin loading = 1.2 mmol.g^{-1}, 0.1 equiv), and purged by argon. Then, dibutyl ether (5 mL), nitrile (2.5 mmol, 1 equiv.), trimethylsilyl azide (432 mg, 497 µL, 3.75 mmol, 1.5 equiv) were introduced. The reaction mixture was stirred under orbital stirring and heated at 140°C under inert atmosphere during 18h. Then, petroleum ether (15 mL) and 1M NaOH solution (5 mL) were added. The polymer was filtered and successively washed with a 1M NaOH solution (5 mL), THF (5 mL) and finally petroleum ether (5 mL). The aqueous phase of the filtrate solution was separated from the organic one and acidified to pH = 1 at 0°C in order to obtain the tetrazole **3** as a solid. After filtration, the white solid was dried under vacuum. A similar procedure was used for the synthesis of 5-substituted-1*H*-tetrazoles catalyzed by **P8** or **P9** (188 mg, tin loading = 1.33 mmol.g^{-1}).

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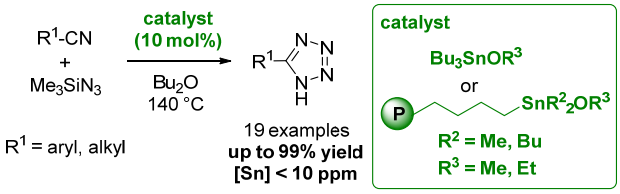
Tin-Catalyzed Synthesis of 5-Substituted *1H*-Tetrazoles from Nitriles:Homogeneous and Heterogeneous procedures



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