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A novel and efficient tributyltin azide-mediated synthesis of 1*H*-tetrazolylstilbenes from cyanostilbenes

Narsimha Reddy Penthala, Shobanbabu Bommagani, Jaishankar Yadlapalli, Peter A. Crooks *

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

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ABSTRACT

A novel and efficient route was established for the synthesis of a series of (*Z*)-5-(2-(heteroaryl-2-yl) and (*Z*)-5-(3-(heteroaryl-3-yl)-1-(phenyl)vinyl)-1*H*-tetrazoles (**3a**–**g** and **6a**–**f**, respectively) from cyanostilbene analogs containing benzo[*b*]thiophene, benzo[*b*]furan, and indole moieties utilizing tributyltin azide as a Lewis acid. This 1,3-dipolar [3+2]cycloaddition of azide to the cyano group of the cyanostilbene precursor molecule affords good yields of the corresponding tetrazolylstilbene analog and constitutes a simple and cost-effective procedure.

The chemistry of tetrazoles has acquired immense importance in recent years,[1] since the tetrazole moiety is a metabolically stable structure and has similar acidic character (i.e. is bioisosteric) with the carboxylic acid moiety[2] but is more resistant to many of the biological transformations that the carboxylic acid functionality is susceptible to in the liver.[3] The tetrazoles are ionized at physiological pH (7.4) like their carboxylic acid counterparts, and the anionic tetrazoles are nearly 10 times more lipophilic than their corresponding carboxylates,[4] which is an important factor with regard to permeation of drug molecules through cell membranes. The synthesis of 5-substituted-1*H*-tetrazoles by conventional approaches has been reported to proceed via [3+2]cycloaddition of azide with nitriles.[5] Many protocols are available for the preparation of 5-substituted tetrazoles from aromatic nitriles by utilizing different azides such as silicon or tin azide,[6–8] Trimethylsilyl azide (TMSA)[9] and sodium azide in combination with different Lewis acid catalysts.[10–12] Several homogeneous catalysts, i.e. Zn $(OTf)_3$,[13] $AlCl_3$,[14] $Pd(PPh_3)_4$[15] $BF_3.OEt_2$,[11] $Pd(OAc)_2/ZnBr_2$,[16] Yb $(OTf)_3$,[17] and various heterogeneous catalytic systems, such as $FeCl_3/SiO_2$,[18] γ-Fe_2O_3,[19] ZnS,[20] $CdCl_2$,[21] Zn/AlHT,[22] natural natrolite zeolite,[23] Zn hydroxyapatite,[24] and Cu_2O[25,26] have also been reported for the synthesis of tetrazoles. However, there have been no reports on the conversion of the acrylonitrile moiety to 5-substituted 1*H*-tetrazoles.

In this Letter, we describe the synthesis of a series of (*Z*)-5-(2-(heteroaryl-2-yl) and (*Z*)-5-(3-(heteroaryl-3-yl)-1-(phe-nyl)vinyl)-1*H*-tetrazoles from acrylonitrile precursor molecules utilizing tributyltin azide (Bu_3SnN_3) as an azidation reagent.

Bu_3SnN_3 is a covalently linked azide similar to TMSA and diphenylphosphoryl azide (DPPA) that mediates azidation reactions in fairly homopolar solvents. Although Bu_3SnN_3 is toxic in nature it is a popular reagent for the synthesis of many organic compounds,[27–31] including tetrazoles,[8,32,33] owing to its solubility in organic solvents, which can safely provide high azide concentrations in solution. Convenient in situ generation, thermal stability, and ease of hydrolysis are also additional merits of using Bu_3SnN_3. In addition, conventional tetrazole-yielding reactions are generally slow because of the biphasic reaction system involving NaN_3 and nitriles. Bu_3SnN_3 affords excellent yields[8] of tetrazoles, and is a particularly effective reagent[33] for the conversion of sterically hindered nitriles to tetrazoles in comparison to the other reagents such as TMSA, alkyl azides, or NaN_3/NH_4Cl.[8]

Recently, we have reported on the synthesis and anti-cancer activity of a series of novel triazole analogs of heteroaromatic cyanostilbenes where the triazole unit has been incorporated as a bridge between the two aromatic ring systems in the molecule by chemical transformation of the cyanostilbene moiety.[34–37] We have now developed a convenient and viable process for the preparation of novel tetrazolylstilbene derivatives via chemical modification of the cyano moiety of a series of heteroaromatic cyanostilbenes that have previously been reported as potent anticancer agents that target tubulin polymerization.[38,39]

We focused on the formation of 1*H*-tetrazolyl analogs because these tetrazole-tethered stilbene analogs are predicted to have improved drug-likeness in comparison to the previously reported[34]

* Corresponding author. Tel.: +1 501 686 6495; fax: +1 501 686 6057.
E-mail address: PACrooks@uams.edu (P.A. Crooks).

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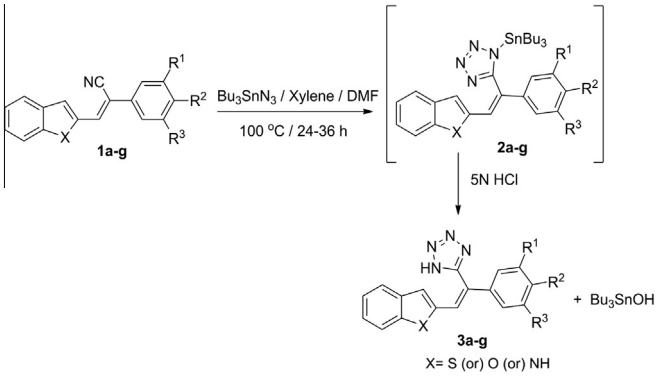
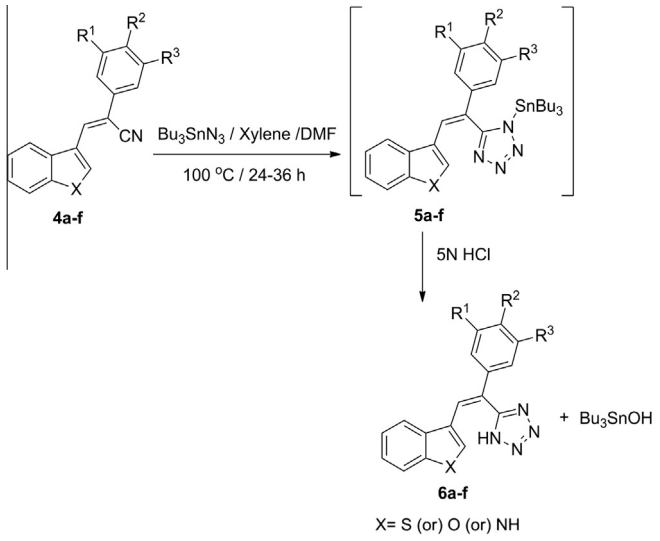


Scheme 1. Synthesis of (*Z*)-5-(2-(heteroaryl-2-yl)-1-(phenyl)vinyl)-1*H*-tetrazoles (**3a**–**g**).

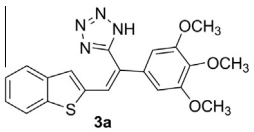


Scheme 2. Synthesis (*Z*)-5-(2-(heteroaryl-3-yl)-1-(phenyl)vinyl)-1*H*-tetrazoles (**6a**–**f**).

triazole analogs of this type. It is well known that tetrazolyl moieties are unique because of their acidity (pKa ~5). The tetrazolyl moiety is bioisosteric with the carboxylic acid moiety, has a similar pKa value as acetic acid and other aliphatic carboxylic acids, and is often utilized in drug design to improve druglikeness and water solubility.[40,41] Thus, because of their acidity, molecules containing a tetrazolyl moiety can exist as a water-soluble sodium tetrazolate salt form. On the other hand, the triazolyl moiety is only weakly acidic (pKa ~8–10) with acidities comparable to β-ketoesters or 1,3-diketo compounds. The pKa value more clearly shows the differences in physical properties of the two scaffolds and the predicted usefulness of the more water-soluble tetrazole derivatives as their sodium salts when compared to the triazole derivatives. In this regard we have provided the comparative pKa values for the tetrazole and triazole analogs in the supporting information to justify our prediction of improved druglikeness of the tetrazole analogs over the triazole analogs. In the present communication three heteroaromatic cyano-stilbene scaffolds have been utilized, i.e. (*Z*)-3-(benzo[*b*]thio-phenyl)-2-phenylacrylonitrile, (*Z*)-3-(benzo[*b*]-furan)-2-phenyl-acrylonitrile and (*Z*)-3-(indole)-2-phenyl-acrylonitrile ring systems. These heteroaromatic stilbenes systems have a cyano group at the sp2 carbon adjacent to the phenyl substituent which can be chemically transformed into a tetrazole moiety to afford novel tetrazolylstilbenes. We have developed a two-step procedure for the synthesis of a variety of such stilbenes. In the first step of the synthesis, heteroaromatic aldehydes have been reacted with variously substituted phenyl acetonitriles in 5% sodium methoxide/methanol solution at reflux temperatures over 4–6 h to obtain the intermediate hetero aromatic cyanostilbene analogs via previously reported procedures.[38,39] In step 2, these cyanostilbene intermediates have then been reacted with tributyltin azide (Bu_3SnN_3) formed in situ from the reaction of NaN_3 with tributyltin chloride, followed by hydrolysis of the resulting tetrazolylstilbene-tributyltin complex in 5 N HCl at room temperature to afford the corresponding (*Z*)-5-(heteroaryl)-1-(phenyl)-vinyl)-1*H*-tetrazole analog (Schemes 1 and 2).

Initial optimization studies on the conversion of the cyano group of the cyanostilbene moiety to a 5-substituted 1*H*-tetrazole moiety were studied utilizing NaN_3 in the presence of NH_4Cl or Bu_3SnCl as catalysts and a variety of solvents (*o*-xylene, DMF, DMSO and water) at 100–130 °C. We utilized the synthesis of compound **3a** from **1a** as a model reaction (Table 1). Refluxing (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl)-acryl-onitrile (**1a**) with NaN_3 in a mixture of DMF and water (4:1) for 36 h afforded poor yields of the tetrazole product **3a** (Table 1, entry 1). Addition of NH_4Cl led to a modest improvement in yield (entry 2). Previous reports on the synthesis of tetrazoles clearly specify that DMSO,[42] DMF,[22,42] water,[10] or *o*-xylene and DMF[33] are the most suitable solvents for these reactions, presumably due to the high boiling point and improved solubility of the reagents in these solvents. The use of Bu_3SnCl as a Lewis acid catalyst in these reac-

Table 1
Different reaction conditions and yields for the formation of **3a** from (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl)-acrylonitrile (**1a**)



Entry	Reagent (3 mol. equiv)	Solvent	NaN_3 (equiv)	Temp (°C)	Time (h)	Yield (%)
1	–	DMF + H_2O (4:1)	2	120	36	10
2	NH_4Cl	DMF	2	120	24	25
3	NH_4Cl	DMF + H_2O (4:1)	3	120	24	34
4	NH_4Cl	DMF + H_2O (4:1)	2	120	24	40
5	Bu_3SnCl	DMSO	1	120	24	55
6	Bu_3SnCl	*o*-Xylene	1	100	24	30
7	Bu_3SnCl	*o*-Xylene	1	130	24	25
8	Bu_3SnCl	*o*-Xylene + DMF (3:1)	2	100	24	80
9	Bu_3SnCl	*o*-Xylene + DMF (3:1)	3	100	24	90
10	Bu_3SnCl	*o*-Xylene + DMF (3:1)	3	100	15	81
11	Bu_3SnCl	*o*-Xylene + DMF (3:1)	3	130	24	85
12	Bu_3SnCl	*o*-Xylene + DMF (3:1)	3	100	36	80

Table 2
(*Z*)-5-(2-(hetero-2-yl)-1-(phenyl)vinyl-1*H*-tetrazoles (**3a–g**), their reaction times and yields

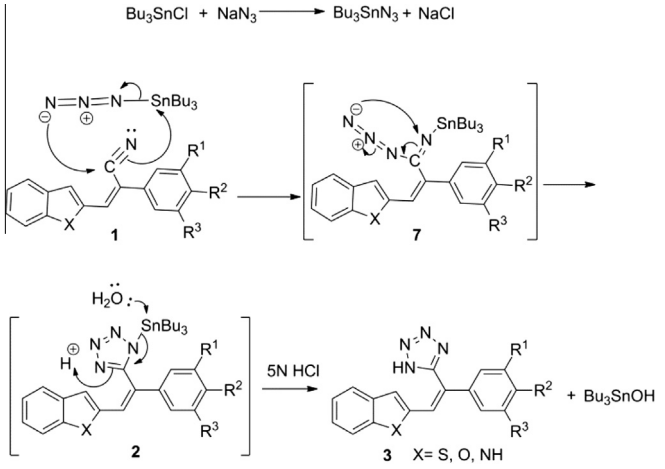
Compound	X	R^1	R^2	R^3	Time (h)	Yield (%)
3a	S	OCH_3	OCH_3	OCH_3	24	90
3b	S	OCH_3	H	OCH_3	30	88
3c	S	OCH_3	OCH_3	H	30	82
3d	S	H	OCH_3	H	36	80
3e	S	OCH_3	OH	OCH_3	36	77
3f	O	OCH_3	OCH_3	H	36	70
3g	NH	OCH_3	OCH_3	OCH_3	30	78

tions significantly improved product yields. A variety of reaction conditions and solvents were investigated and it was found that utilizing 2–3 molar equivalents of NaN_3 in a mixture of *o*-xylene and DMF afforded yields of **3a** in the range 80–90% (Table 1). The use of only *o*-xylene in the above reaction afforded low yields because of the low solubility of the reactants in this solvent. Refluxing **1a** with NaN_3 (3 mol. equiv) in the presence of Bu_3SnCl (3 mol. equiv) in *o*-xylene/DMF at 100 °C for 24 h followed by hydrolysis of the resulting tetrazole-$SnBu_3$ complex in 5 N HCl afforded a 90% yield of product **3a** (Table 1, entry 9).

Various (*Z*)-3-(heteroaryl-2-yl)-2-(phenyl)-acrylonitrile analogs (**1a–g**) and Bu_3SnN_3 (prepared in situ from sodium azide and tributyltin chloride) were refluxed for 24–36 h in a mixture of *o*-xylene/DMF at 100 °C to afford the corresponding (*Z*)-5-(heteroaryl-2-yl)-1-(phenyl)-vinyl)-1*H*-tetrazole-tributyltin azide intermediates **2a–g**, which were then hydrolyzed in the presence of 5 N HCl at room temperature to yield the desired tetrazolyl stilbenes **3a–g** (Scheme 1) in 70–90% yields (Table 2). Similarly, the isomeric heteroaryl-3-yl cyanostilbenes **4a–f** were converted into their corresponding (*Z*)-heteroaryl-3-yl tetrazolylstilbenes **6a–f** via azide intermediates **5a–f** (Scheme 2, Table 3) in 72–91% yield. The structure and purity of the products were verified by ^{1}H- and ^{13}C NMR spectroscopy and by HPLC (1:1 water and ACN with 0.1% of formic acid at 0.5 ml/min flow rate using C-18 column). The double bond geometry was also confirmed as *Z*-isomer by single-crystal X-ray analysis (Fig. 1).

Table 3
Various (*Z*)-5-(2-(heteroaryl-3-yl)-1-(phenyl)vinyl)-1*H*-tetrazoles (**6a–f**) and their reaction times and yields

Entry	X	R^1	R^2	R^3	Time (h)	Yield (%)
6a	S	OCH_3	OCH_3	OCH_3	24	91
6b	S	OCH_3	H	OCH_3	30	87
6c	S	OCH_3	OCH_3	H	30	85
6d	S	H	OCH_3	H	36	80
6e	O	OCH_3	H	OCH_3	36	72
6f	NH	OCH_3	H	OCH_3	36	84



Scheme 3. Plausible mechanism for the formation of tetrazolyl -stilbenes **3** from their cyanostilbene precursors **1**.

Increasing the number of electron-releasing methoxy substituents on the phenyl ring of the cyanostilbene precursor generally increased the rate of the reaction and the yield of the corresponding tetrazolylstilbene products, which is consistent with previous studies by Sisido et al.,[32] who reported that trialkyltin azides react more readily with aromatic nitriles containing electron-releasing substituents than with those containing electron-withdrawing groups.

A plausible mechanism for the formation of the above tetrazolylstilbenes from their precursor cyanostilbenes is shown in Scheme 3. The initial attack of Bu_3SnN_3 on the cyano group of **1** occurs to form intermediate **7** as has been proposed by Aureggi and Sedelmeier,[33] which then undergoes cyclization by formation of an N–N covalent bond between the nitrogen atom of azide moiety and the nitrogen atom attached to tributyltin, resulting in the formation of tetrazole-tributyltin intermediate **2**. Hydrolysis of **2** in 5 N HCl then affords tetrazolylstilbene **3**, with elimination of tributyltin hydroxide.

In conclusion, a novel and efficient route of synthesis has been developed for the synthesis of a series of (*Z*)-5-(2-(heteroaryl-2-yl) and (*Z*)-5-(3-(heteroaryl-3-yl)-1-(phenyl)vinyl)-1*H*-tetrazoles (**3a–g** and **6a–f**, respectively) that incorporate benzo[*b*]thio-phenyl, benzo[*b*]furanyl, and indolyl moieties. These products were formed from cyanostilbene precursors via a tributyltin azide-mediated [3+2]cycloaddition reaction. This method provides an efficient, simple, and cost-effective procedure for the synthesis of novel tetrazolylstilbenes in high yields.

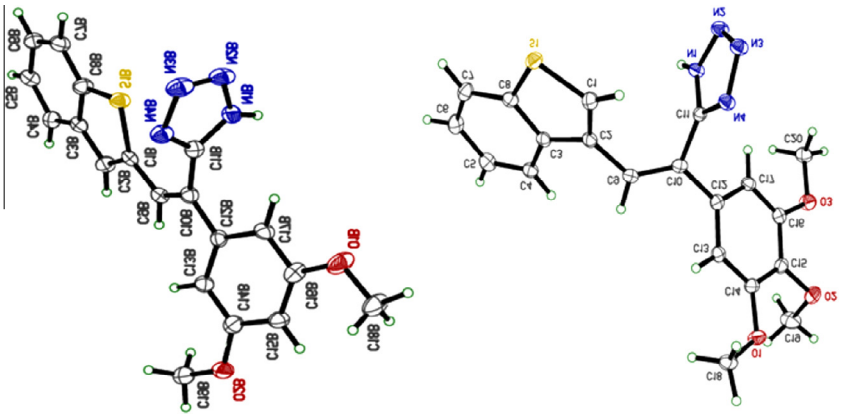


Figure 1. Representative single crystal X-ray structures of (*Z*)-5-(2-(benzo[*b*]thiophen-2-yl)-1-(3,5-dimethoxyphenyl)vinyl-1*H*-tetrazole (**3b**) and (*Z*)-5-(2-(benzo[*b*]thiophen-3-yl)-1-(3,4,5-trimethoxy-phenyl)vinyl)-1*H*-tetrazole (**6a**).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.040.

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