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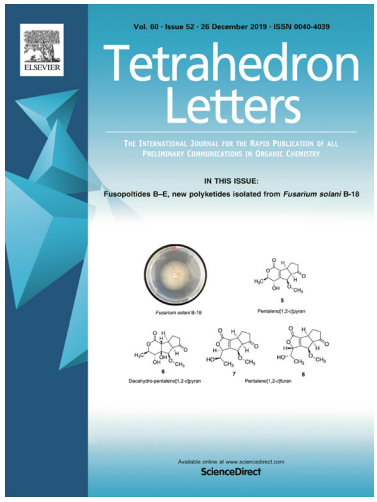

$TMSN_3$-$Bu_2Sn(OAc)_2$: A modified and mild reagent system for Wittenberger tetrazole-synthesis

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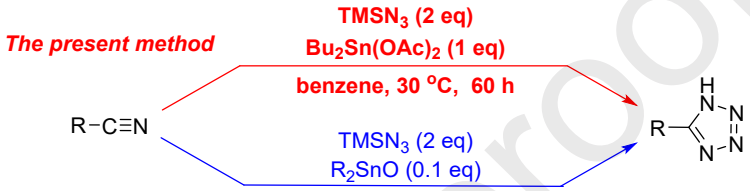

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$TMSN_3$-$Bu_2Sn(OAc)_2$: A modified and mild reagent system for Wittenberger tetrazole-synthesis

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ABSTRACT

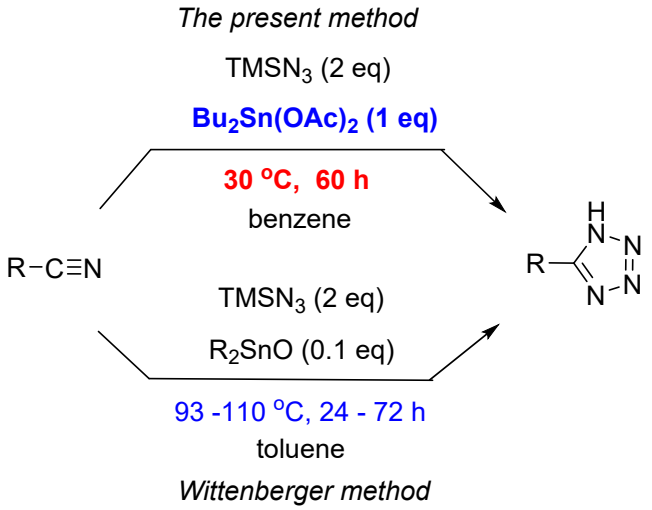
Treatments of various nitriles with $TMSN_3$ and $Bu_2Sn(OAc)_2$ at 30 °C in benzene for 60 h yielded the corresponding 5-substituted 1*H*-tetrazoles in good to excellent yields. This method is a mild and efficient alternative reagent system for Wittenberger tetrazole-synthesis that uses $TMSN_3$ and Bu_2SnO in toluene at high temperature (93–110 °C) for 24–72 h.

1. Introduction

Tetrazoles are useful in various applications owing to their wide-ranging potentials in a variety of different fields.[1] 1*H*-Tetrazoles have long been recognized as metabolically stable bioisosteres of carboxylate groups.[1] In medicinal chemistry, this property has been notably popularized in anti-hypertensive drugs that include losartan, candesartan, and valsartan which contain the 5-(4'-methyl-1,1'-biphenyl-2-yl)-1*H*-biphenyl tetrazole subunit.[1] Furthermore, due to the chemical instabilities of these nitrogen-rich heterocycles, they have been exploited as components of explosives.[1]

5-Substituted 1*H*-tetrazoles are basically synthesized by the [2+3] cycloaddition of nitriles and azides,[2] which only takes place at a sufficient rate if electron-withdrawing groups are present on the nitrile. Many of the established approaches for [2+3] cycloadditions are still severely limited in their use due to a lack of generality, including high temperatures >100 °C, longer reaction times, the use of microwave (MW) irradiations, and lower yields.[2]

Among the above-mentioned methods, in 1993 Wittenberger reported an efficient method for the preparation of 5-substituted 1*H*-tetrazoles from nitriles that uses trimethylsilyl azide ($TMSN_3$, 2 eq.) as a comparatively safe azide source in the presence of catalytic dibutyltin oxide or dimethyltin oxide (Bu_2SnO or Me_2SnO, 0.1 eq) (Scheme 1, bottom).[3] The mechanism of the Bu_2SnO-catalyzed $TMSN_3$-nitrile cycloaddition has been also studied in detail.[4] Unfortunately, the Wittenberger conditions for aromatic or less-reactive alkyl nitriles requires long reaction times (24–72 h) and high temperatures (93–110 °C) to form the corresponding aromatic or alkyltetrazoles.[3] In this paper, we describe a modified and mild reagent system for the Wittenberger tetrazole-synthesis that uses $TMSN_3$ (2 eq) and dibutyltin diacetate ($Bu_2Sn(OAc)_2$, 1 eq). This methodology provides both 5-aromatic and aliphatic 1*H*-tetrazoles in good-to-excellent yields under safer reaction conditions (30 °C , 60 h, benzene).



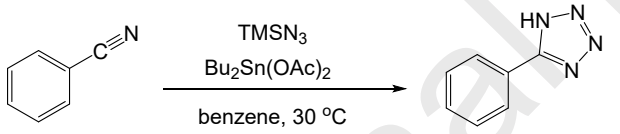
Scheme 1. The Wittenberg tetrazole-synthesis and our method.

2. Results and discussion

Although Bu_2SnO (DBTO)[5] is usually used as the organotin catalyst in the Wittenberger method, the low solubility of solid DBTO (mp: 105 °C) in most solvents appears to be partially responsible for the need for refluxing toluene.[6] The use of an alternative organotin compound that more-easily dissolves in a variety of solvents may lead to tetrazole formation under milder reaction conditions. From this viewpoint, we directed our attention to dibutyltin diacetate [$Bu_2Sn(OAc)_2$; b.p.: 130 °C (5 mmHg)], which is a liquid at room temperature (rt) and is used as a stabilizer for chlorinated organics, and as a catalyst for condensation reactions.[7]

We first investigated the reaction of benzonitrile (**1a**) with $TMSN_3$ (1 eq) in the presence of a catalytic amount of $Bu_2Sn(OAc)_2$ (0.1 eq) at 30 °C in benzene, which produced 5-phenyltetrazole (**2a**) in 28% yield after 24 h, as shown in entry 1 of Table 1. This result suggests that $Bu_2Sn(OAc)_2$ can be used as an alternate reagent to DBTO. Increasing the amount of $Bu_2Sn(OAc)_2$ (1 eq) as well as extention of the reaction time (60 h) were effective in provided improved yields (71%) of **2a** (entry 3). In particular, when **1a** was reacted with $TMSN_3$ (2 eq) in the presence of $Bu_2Sn(OAc)_2$ (1 eq) in benzene at 30 °C for 60 h, tetrazole **2a** was produced in 99% yield (entry 6), while the reaction at 15 °C for 60 h gave **2a** in only 50% yield (entry 7). This result suggests that a reaction temperature of about 30 °C is necessary for the conversions of nitriles **1** into tetrazoles **2**. Since tetrazole **2a** settles as a while precipitate in the flask as the reaction progresses in these cases, it was easily separated by filtration [see Supplementary Data (S. D.)].

Table 1. Formation of 5-phenyltetrazole from benzonitrile using $TMSN_3$/ $Bu_2Sn(OAc)_2$.



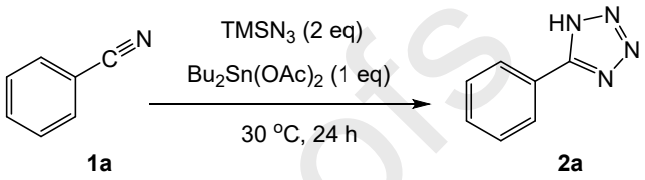
entry	$TMSN_3$ (eq)	$Bu_2Sn(OAc)_2$ (eq)	time (h)	**2a** (%)
1	1	0.1	24	28
2	1	1	24	43
3	1	1	60	71
4	2	1	24	73
5	2	1	48	86
6	2	1	60	99
7[a]	2	1	60	50

a) Reaction temperature: 15 ° C

The effect of solvent on the reaction was also investigated for a reaction time of 24 h (Table 2). Toluene can be used as an alternative solvent to give **2a** in 64% yield (entry 2), while dichloromethane, methanol, and THF led to lower yields of **2a** (entries 3–5), compared to the reactions performed in benzene or toluene. When acetonitrile was used as solvent, **2a** was obtained in 40% yield, along with 5-methyltetrazole (40%) (entry 6), which nitriles.[8] Thus, the optimized procedure (Table 1, entry 6) was obtained from Table 1 and 2.

Meanwhile, the formation of **2a** from **1a** using the Wittenberger method [$TMSN_3$ (2 eq), BDTO (0.1 eq)] required heating at 93 °C in toluene for 72 h to give **2a** in 60% yield.[3] Furthermore, in contrast, the reaction of **1a** with $TMSN_3$ (2 eq)/DBTO (1 eq) in benzene at 30 °C for 60 h resulted in only the unreacted starting material **1a** (see S. D.).

Table 2. Formation of 5-phenyltetrazole **2a** from benzonitrile **1a** in various solvents.



entry	solvent	**2a** (%)
1	benzene	73
2	toluene	64
3	CH_2Cl_2	58
4	MeOH	31
5	THF	58
6	CH_3CN	40 [a]

a) The formation of 5-methyltetrazole (40%) was accompanied by **2a** (40%).

Using the optimized procedure [$TMSN_3$ (2 eq)/$Bu_2Sn(OAc)_2$ (1 eq), benzene, 30 °C, 60 h], many nitriles **1** were transformed into various 5-substituted tetrazoles **2**, as summarized in Table 3 (see S. D.). 4'-Functionalized phenyltetrazoles **2b**–**e** [X = MeO, Me_2N, NO_2, and $CH_3C(O)$] were readily obtained from the corresponding nitriles **1b**–**e** in yields of 82–99%. 2-Bromobenzonitrile **1f** was transformed into 5-(2-bromophenyl)tetrazole **2f** in 40% yield under these conditions (30 °C for 60 h), while 50 °C for 60 h gave a better yield (78%) of **2f**. 3-Bromobenzonitrile **1g** was converted into the corresponding tetrazole **2g** at 30 °C in 78% yield. Meanwhile, application of the Wittenberger method [$TMSN_3$ (2 eq), Me_2SnO (0.1 eq)] to **1f** and **1g** gave **2f** and **2g** in 74% and 80% yields, respectively, at 93 °C for 72 h.[3] Using the present method, phenyltetrazoles **2b-e** and **2g** produced white precipitates that were easily worked up (see S. D.).

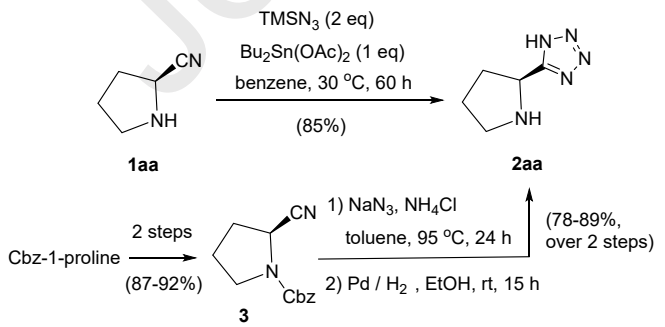
Alkylnitriles **1h** and **1i**, which are deactivated by electron-donating alkyl groups, gave better yields of 5-substituted alkyltetrazoles **2h** (89%) and **2i** (89%), respectively, under the standard conditions, compared to those (85% and 50%) produced by the Wittenberger method in refluxing toluene for 25 h.[3] Cyclohexanecarbonitrile **1j** as well as functionalized acetonitriles **1k** (X = OMe), **1l** (X = F), and **1m** (X = CF_3) afforded high yields of the corresponding tetrazoles **2j** (93%), **2k** (99%), **2l** (99%), and **2m** (99%). 1,2-Di(1*H*-tetrazol-5-yl)ethane **2n**[8] was also prepared

in m
method.

Transformation of nitrile **1o** bearing terminal alkyne and ester moieties into the corresponding tetrazole **2o** proceeded smoothly in 98% yield. The results demonstrate that the present method is relatively tolerant toward nitriles bearing a range of functional groups.

The potential of this reaction was further explored by applying it to the synthesis of tetrazole-containing biofunctional molecules. We previously attempted to prepare tetrazoles **2p** and **2q** as ligands for Pt(II) complexes that exhibit antitumor activities,[8,9] in which reactions of ethyl cyanoformate (**1p**: n = 1, m = 0) or propyl cyanoacetate (**1q**: n = 2, m = 1) with NaN_3 in the presence of $Et_3N{\cdot}HCl$ in DMF with MW irradiation (130 °C, 2 h) resulted only in decomposition of the products.[8] In contrast, the present method easily provided the desired tetrazoles **2p** (99%) and **2q** (99%) from **1p** and **1q**. Furthermore, four aliphatic tetrazoles (**2r-u**) containing adamantane as Pt(II)-ligands were prepared from the corresponding nitriles (**1r**–**u**) in yields of 71–99%.[9]

The present method was also applied to the synthesis of 3-(tetrazol-5-yl)-3,5-pregnadien-20-one (**2v**) which is a potent 5α-reductase inhibitor (IC_{50}: 15.6 nM).[10] When 3-cyano-3,5-pregnadien-20-one (**1v**) was subjected to the present method, diene tetrazole **2v** was produced in 58% yield, while the transformation of **1v** into **2v** using NaN_3-$Et_3N{\cdot}HCl$ or $TMSN_3$ (2 eq)-DBTO (0.1 eq) required refluxing toluene for 24 h to give **2v** in 67% or 98% yield, respectively.[10] In our study for probing RNA catalysis,[11, 12] tetrazole C5-linked C_0- and C_2-ribonucleosides **2w** (n = 0) and **2x** (n = 2) were synthesized, in which **2x** was obtained from the normally inactive alkylcyanide **1x** under MW irradiation conditions (NaN_3-$Et_3N{\cdot}HCl$, 130 °C, 2 h, DMF) in 95% yield.[8,12] Tetrazole **2w** (n = 0) was easily prepared in 92% yield by the present method from the active sugar nitrile **1w**, while the transformation of inactive alkylnitrile **1x** (n = 2) gave a moderate yield (52%) of tetrazole **2x**. Furthermore, the synthesis of 5-(4'-methyl-1,1'-biphenyl-2-yl)-1*H*-tetrazol (**2y**) is of particular interest because it represents the basic structure of most angiotensin II antagonists.[1,2] However, the reaction produced only 5% yield of **2y** at 30 °C for 60 h, while an improved yield (58%) was obtained at 50 °C. The methylester precursor **2z** of valsartan[1,2] was similarly produced from nitrile **1z** in 41% yield at 50 °C, with the starting **1z** (58%). In addition, l-pyrrolidine-2-yl-1*H*-tetrazole (**2aa**), which is a proline-derived organocatalyst for a variety of reactions,[13] is usually prepared in four steps from benzyloxycarbonyl(Cbz)-L-proline via *N*-Cbz-L-prolinamide (**3**), as illustrated in Scheme 2.[13a] Interestingly, the present method directly afforded **2aa** from commercially available (*S*)-pyrrolidine-2-carbonitrile (**1aa**) in 85% yield.



Scheme 2. Comparing the present and previous methods for the synthesis of l-pyrrolidine-2-yl-1*H*-tetrazole (**2aa**).

In this study, we demonstrated that the $TMSN_3$/$Bu_2Sn(OAc)_2$ method furnishes 5-substituted 1*H*-tetrazoles from a variety of nitriles at 30 °C for 60 h in good to excellent yields, when compared to the Wittenberger conditions that require higher temperatures. Although many current methods use reaction temperatures above 100 °C,[2] the developed method avoids these harsh conditions, which is important for the preparation of explosive tetrazoles. Therefore, the present method is flexible and broadly applicable to the synthesis of tetrazole.

Acknowledgments

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Supplementary Data

Supplementary data for this article can be found online at --------.

References and notes

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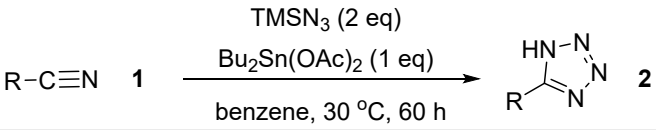
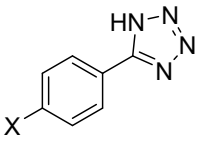
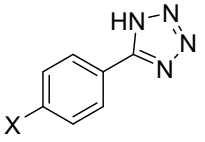
Table 3. Transformation of nitriles **1** into 5-substituted tetrazoles **2** by the present method

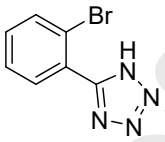




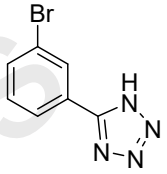
2b, X = MeO : 82%
2c, X = Me_2N: 90%



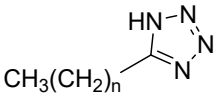
2d, X = NO_2: 93%
2e, X = MeC(O): 99%



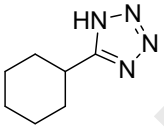
2f, 78%[a] (74%)[b]



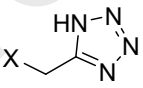
2g, 78% (80%)[b]



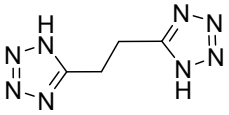
2h, *n* = 3: 89% (85%)[c]
2i, *n* = 4: 89% (50%)[c]



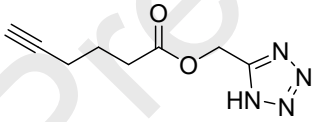
2j, 93%



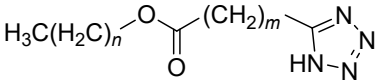
2k, X = OMe: 99%
2l, X = F: 99%
2m, X = CF_3: 99%



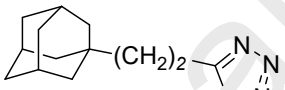
2n, 67%



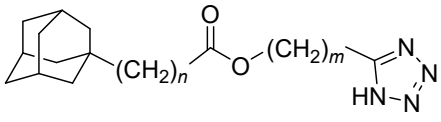
2o, 98%



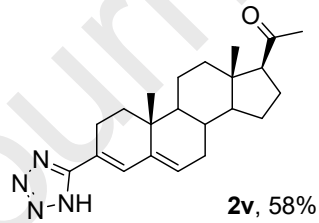
2p, *n* = 1, m = 0: 99%
2q, *n* = 2: m = 1: 99%



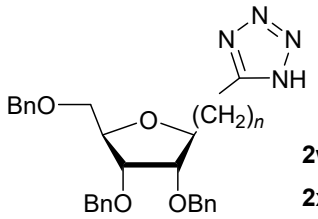
2r, 71%



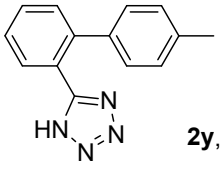
2s, *n* = 0, m = 1: 99%
2t, *n* = 0: m = 2: 95%
2u, *n* = 1: m = 1: 86%



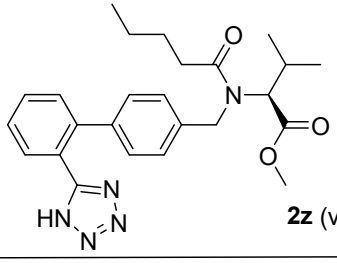
2v, 58% (67%[d]; 98%[c])



2w, *n* = 0 : 92%
2x, *n*= 2; 52% (95%[e])



2y, 58%[a]



2z (valsartan-methyl ester), 41%[a]

a) $TMSN_3$ (2 eq), $Bu_2Sn(OAc)_2$ (1 eq), toluene, 50 °C, 60 h.

b) $TMSN_3$ (2 eq), Me_2SnO (0.1 eq), toluene, 93 °C, 72 h.

c) $TMSN_3$ (2 eq), Bu_2SnO (0.1 eq), toluene, 110 °C, 25 h.

d) NaN_3 (3 eq), $Et_3N{\cdot}HCl$ (3 eq), toluene, 110 °C, 24 h.

e) NaN_3 (3 eq), $Et_3N{\cdot}HCl$ (3 eq), DMF, MW, 130 °C, 2 h.

Highlights

1. The present tetrazole synthesis uses $TMSN_3$ and $Bu_2Sn(OAc)_2$ at 30 °C.

2. This method is an alternative reagent system for Wittenberger tetrazole-synthesis.

3. This method may avoid harsh conditions for the preparation of explosive tetrazoles.