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Antimony Trioxide as an Efficient Lewis Acid Catalyst for the Synthesis of 5-Substituted 1*H*-Tetrazoles

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Abstract: Sb_2O_3 was found to be effective as a catalyst for a smooth (2+3) cycloaddition of sodium azide with nitriles to afford 5-substituted 1*H*-tetrazoles in good yields.

Keywords: Sb₂O₃, sodium azide, 5-substituted 1H-tetrazoles

INTRODUCTION

Tetrazoles, a class of heterocycles, received considerable attention because of their wide range of applications in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates and in speciality explosives, photography, and information recording systems.^[1] They are important ligands for many useful transformations and also precursors for a variety of nitrogen-containing heterocycles.^[2] Losartan, irbesartan, candesartan, and valsartan are famous antihypertensive drugs belonging to the class of nonpeptide angiotensin-II inhibitors, which prevent increases in blood pressure; they have biphenyl tetrazolyl moiety in their structure. Derivatives of tetrazoles are also used for biological activities such as antiviral, antibacterial, antifungal, and antituberculous activities. In addition to this, tetrazoles are used as catalysts in the synthesis of phosphonates.

Conventionally 5-substituted 1*H*-tetrazoles are synthesized via (2+3) cycloaddition of an azide and a nitrile.^[3] The reagents used in the basic method are highly toxic and expensive and are also water sensitive. In

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addition to this, hydrazoic acid is not only highly toxic and explosive but also volatile. To overcome the drawbacks of the earlier methods, attention has been paid to developing safer and neat methods for the synthesis of tetrazoles. Accordingly 5-substituted tetrazoles are also prepared through the reaction of sodium azide with corresponding nitriles in the presence of an amine salt.^[4] Demko and Sharpless and coworkers reported an innovative and safe procedure for the synthesis of tetrazoles by the addition of sodium azide to nitriles using stoichiometric amounts of Zn(II) salts in water.^[5] Amantini et al. efficiently synthesized tetrazoles by the addition of TMSN₃ (trimethyl silyl azide) to organic nitriles using 10 mol% TBAF (tetra butyl ammonium fluoride) as catalyst.^[6] Su et al.^[7] reported a series of 1-substituted 1H-1.2,3,4-tetrazole compounds that have been synthesized in good yields from amines, triethyl orthoformate, and sodium azide through the catalyzed reaction with Yb(OTf)₃. A series of primary alcohols and aldehydes were treated with iodine in ammonia water under microwave irradiation to give the intermediate nitriles, which without isolation underwent [2+3] cycloaddition with dicyandiamide and sodium azide to afford the corresponding triazines and tetrazoles in high yields.^[8] Katritzky and coworkers^[9] suggested a general method for the synthesis of 1,5-disubstituted tetrazoles from imidoylbenzotriazoles under mild reaction conditions and shorter reaction times. A versatile and highly efficient Zn(OTf)₂-mediated one-pot synthesis of 1.5-disubstituted tetrazoles derivatives has been achieved by Hajra et al.^[10] from alkenes, N-bromo succinimide (NBS), nitriles, and TMSN₃. In recent publications,^[11,12] Lakshmi Kantam et al. developed simple and efficient methods for the preparation of 5-substituted 1Htetrazoles via [2+3] cycloaddition using nano ZnO and zinc hydroxyapatite (ZnHAP) as effective catalysts.

Antimony compounds are excellent catalysts to accelerate the polymerization in polyester manufacturing. Even though antimony trioxide is the most widely used polymerization catalyst, to the best of our knowledge, Sb_2O_3 has not been explored as a catalyst for such a transformation previously. In this communication, we report the synthesis of 5-substituted 1H-tetrazoles from a wide variety of organic nitriles with sodium azide using Sb_2O_3 as a Lewis acid catalyst for the first time (Scheme 1).



Scheme 1. Synthesis of 5-substituted 1H-tetrazoles catalyzed by Sb₂O₃.

In an effort to develop a better catalytic system, various reaction parameters were screened for [2+3] cycloaddition of benzonitrile with sodium azide to yield 5-phenyltetrazole and are presented in Table 1. The solvent has a pronounced effect in these reactions (Table 1, entries 1–4), in which dimethyl formamide (DMF) was proved to be the best solvent to give good yields of corresponding tetrazole, whereas dimethyl sulfoxide (DMSO) and NMP provided moderate yields, and water gave poor yields of 5-phenyltetrazole. TMSN₃ is also used in the reaction with benzonitrile in DMF at 120 °C (Table 1, entry 5).

To understand the scope and limitations of Sb_2O_3 -catalyzed [2+3] cycloaddition reaction. various structurally divergent benzonitriles possessing a wide range of functional groups were reacted with sodium azide to give corresponding tetrazoles, and the results are summarized in Table 2. The various nitriles tested are aromatic, heteroaromatic, and aliphatic; the aromatic benzonitriles gave moderate to good yields (Table 2, entries 1-14). 4-Chlorobenzonitriles provided the corresponding tetrazoles with good yield, whereas 2-chlorobenzonitriles gave slightly less yield compared to its para counterpart. This might be due to a more pronounced steric effect of chloro group at the orthoposition (Table 2, entries 2 and 3). Benzonitriles with electron-donating groups such as 4-methoxy benzonitrile and 4-methyl benzonitrile afforded slightly better yields (Table 1, entries 8 and 9) compared with electron-withdrawing groups such as hydroxy, chloro, cyano, bromo, and formyl groups present on the aromatic ring (Table 1, entries 2–7). 4-Formylbenzonitrile gave only 1*H*-tetrazole with carbonyl (aldehyde) functionality untouched (Table 2, entry 4). 1,4-Dicyanobenzene afforded diaddition product (Table 2, entry 7). Aliphatic nitriles such as 4-chlorophenyl

	CN + Azide	\rightarrow	$\overset{H}{\underset{N^{\sim}N}{\overset{H}{\xrightarrow}}}_{N^{\sim}N}$
Entry	Solvent	Azide	Yield $(\%)^b$
1	Water	NaN ₃	39
2	DMF	NaN ₃	86
3	DMSO	NaN ₃	72
4	NMP	NaN ₃	69
5	DMF	TMSN ₃	79

Table 1. Screening of reaction parameters for the formation5-phenyltetrazole a

^{*a*}Reaction conditions: nitrile (1 mmol), NaN₃ (2 mmol), Sb₂O₃ (0.029 g or 0.1 mmol), DMF (5 mL), reaction time (8 h), 120 °C.

^bIsolated yields.

Synthesis of Tetrazoles

	R-I + NaN2	Sb ₂ O ₃	R	
	,	DMF, 120-130 ^O C		N ^{-N}
Entry	Substrate	Temp (°C)	Time (h)	Yield (%)
1	CN	120	8	86
2	CI	N 120	8	87
3	CN	120	10	81
4	онс	CN 120	8	79
5	Br	N 120	8	85
6	НОСС	N 130	10	71
7	NC	N 130	9	79
8	H ₃ CO	CN 120	8	85
9	H ₃ C	N 120	8	86

Table 2. Preparation pf 5-substituted 1H-tetrazoles mediated by Sb_2O_3

(Continued)

Entry	Substrate	Temp (°C)	Time (h)	Yield (%)
10	N CN	120	4	88
11		120	4	82
12	CN	130	20	71
13	CI	130	20	69
14	O S CH ₂ CN	130	18	78

Table 2. Continued

acetonitrile, phenyl acetonitrile, and (phenylsulfonyl) acetonitrile provided moderate yields of corresponding tetrazoles with long duration of time (Table 2, entries 12–14). Heteroaromatic nitriles such as 2-pyridinecarbonitrile and cyanopyrazine gave the corresponding tetrazoles in shorter reaction times with excellent yields (Table 2, entries 10 and 11).

In conclusion, a simple and efficient method was developed for the preparation of 5-substituted 1*H*-tetrazoles via (2 + 3) cycloaddition using an economically cheap Sb₂O₃ catalyst. Various structurally divergent nitriles were reacted with NaN₃ at 120–130 °C to yield the corresponding 5-substituted 1*H*-tetrazoles with moderate to good yields. This methodology may find widespread use in organic synthesis for the preparation of 5-substituted 1*H*-tetrazoles.

EXPERIMENTAL

Typical Procedure for Preparation of 5-Substituted 1H-Tetrazole

 Sb_2O_3 was added (0.029 g or 0.1 mmol) to a mixture of benzonitrile (0.103 g or 1 mmol), sodium azide (0.130 g or 2 mmol) in DMF (5 mL)

and stirred at 120 °C for 12 h. After completion of reaction (as monitored by thin-layer chromatography, TLC), the reaction mixture was treated with ethyl acetate (30 mL) and washed with distilled water, and then the organic layer was treated with 5 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated, and the aqueous layer was again extracted with ethyl acetate (20 mL). The combined organic layers were washed with water and concentrated to give the crude solid crystalline 5-phenyltetrazole. Column chromatography was performed using silica gel (100-200 mesh) to afford pure 5-phenyltetrazole.

¹H NMR (200 MHz, CDCl₃ + DMSO) δ 8.04 (m, 2H), 7.61 (m, 3H); MS (70 eV) m/z (%) 146 (M⁺, 12.65%), 118 (100%), 103 (13.94%), 91 (36.70%), 77 (30.37%), 63 (26.58%), 39(17.72%).

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