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Graphical Abstract





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Silica supported lanthanum triflate mediated synthesis of 5-substituted-1H tetrazoles

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ABSTRACT

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Keywords: 5-Substituted 1H-tetrazoles Ln(OTf)₃- SiO₂ [3+2] cycloaddition Nitriles Sodium azide

Silica supported lanthanum triflate $(Ln(OTf)_3$ - SiO₂) promoted synthesis of 5-substituted *1H*-tetrazoles via [3+2] cycloaddition between aromatic/ heteroaromatic nitriles and sodium azide is a high product yielding, facile and straightforward procedure. Non toxicity, recovery and reusability for three continuous cycles are the noteworthy features of the currently employed heterogeneous catalyst.

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Tetrazoles, rich in nitrogen content and bearing low molecular weight, have gained wide recognition as highly versatile moiety in organic, organometallic and medicinal chemistry. Interest in tetrazole chemistry over the recent decade received momentum as this functionality offers a more favorable pharmacokinetic profile, mainly due to the widespread incorporation of tetrazole scaffold into angiotensin II antagonist structures viz. losartan, valsartan and BMS- 183920 etc.¹ and as metabolically stable carboxylic acid surrogates². Tetrazoles have also been frequently used as lipophilic spacers, ligands, precursors to a variety of nitrogen heterocycles in coordination chemistry^{3,4} and in material sciences including photography, information recording systems, propellants and special explosives⁵.

Several sophisticated strategies have been posited in the literature for the synthesis of the aforementioned molecule. Treatment of primary amines with orthocarboxylic acid esters / azides in presence of varied catalysts viz. imidazolium ionic liquids⁶, Yb(OTf)₃⁷ and In(OTf)₃⁸ yields 1-substituted tetrazoles. [3+2] cycloaddition between organic / inorganic azides or hydrazoic acid and corresponding nitriles produces 5-substituted 1H-tetrazoles. Numerous protocols for this conventional synthesis includes employment of various homogenous catalytic systems such as Cu₂O,⁹ BF₃.OEt₂¹⁰, Pd(OAc)₂/ ZnBr₂,¹¹ Zn(OTf)₃,¹² AlCl₃,¹³ Pd(PPh₃)₄,¹⁴ TMSN₃ / TABF,¹⁵ and boron azides.¹⁶ Much to our dismay, these typical procedures suffer from prolonged reaction time, poor selectivity, high temperature, toxic waste generation, separation and recovery of the catalyst, thereby obviating the need for development of safe heterogeneous catalytic systems. Solid support based heterogeneous catalysts are currently under intense focus as they are capable of driving several impracticable organic transformations faster and under mildest possible conditions. They seek advantages such as easy recovery and recyclability with minimal waste generation when compared with the conventional homogeneous catalysts. Alternatively, numerous heterogeneous catalysts such as ZnS nanospheres,¹⁷ Cu-Zn alloy nanopowder,¹⁸ CoY Zeolite,¹⁹ Sb₂O₃,²⁰ CuFe₂O₄ nanoparticles,²¹ zeolite/ sulfated zirconia,²² CdCl₂,²³ phospomolybdic acid,²⁴ FeCl₃- SiO₂,²⁵ Fe₂O₃,²⁶ BaWO₄,²⁷ Zn/ Al hydrotalcite,²⁸ and amberlyst-15²⁹ were reported in the literature. However, high energy barrier involved for the [3+2] cycloaddition and sluggishness of the reaction except when potent electron withdrawing groups are associated with the nitriles, make some of these protocols synthetically futile necessitating more than 12 hours of heating at higher temperatures. Lack of heat control and reproducibility are amongst few drawbacks of microwave assisted synthesis. Thus, development of highly expedient heterogeneous catalytic system for the synthesis of 5-substitued tetrazoles becomes essentially desirable. Lanthanide triflates, efficient and mild Lewis acids are known to promote diverse organic reactions including Friedel- Crafts, Baylis Hillman, aromatic nitration, and Diels-Alder reactions in catalytic quantities.

In our zest to explore and develop synthetic protocols involving environmentally benign and reusable heterogeneous catalysts, we report herein silica supported $Ln(OTf)_3$ mediated synthesis of 5-substituted-*1H* tetrazole via [3+2] cycloaddition between sodium azide and various aromatic nitriles.³⁰ This protocol offers several advantages over the existing methods such as safe alternative to hazardous hydrazoic acid, higher yields in



Scheme 1: Synthesis of 5-substitued tetrazoles via [3+2] cycloaddition between nitriles and sodium azide

comparably shorter reaction time, use of $Ln(OTf)_3$ as a mild lewis acid catalyst, ease of separation and reusability of the catalyst in comparison to homogneous systems and good generality and efficiency towards a wide of range of substrates.

In an effort to develop an innovative and efficient heterogeneous catalytic system for [3+2] cycloaddition between benzonitrile and sodium azide to yield 5- phenyl-*1H* tetrazole, we have examined various parameters such as efficiency of the catalyst and its reusability, effective catalyst loading, solvent and temperature effect.

In order to get an insight into the effect of catalyst on the yield of 5-phenyl-1H tetrazole, different silica supported Lewis acids such as BiCl₃-SiO₂, Ln(OTf)₃-SiO₂, SbCl₃-SiO₂ (Table 1) were screened. Our investigations revealed that, Ln(OTf)₃-SiO₂ in DMF: MeOH (4:1) at 100 °C was by far the most sustainable catalytic system that afforded the desired product in comparably higher yields. The needfulness of the catalyst was realized, when the controlled reaction conducted under identical conditions devoid of Ln(OTf)₃-SiO₂ gave no addition product, despite prolonged reaction time. Catalyst loading was yet another essential factor favoring the yield of the reaction. Use of 200mg of catalyst rendered maximum product yield of 88 % (Table 1). Lower conversions (65- 72%) were obtained when amount of catalyst used was 100mg to 150mg, whereas, further increase in the amount of catalyst did not show any considerable improvement in the yield.

Table1.Effect of various reaction parameters on the formation of tetrazoles 3a from $1a^a$

Entry	Catalyst	Solvent (ratio)	Yield ^b (%)
1	BiCl ₃ -SiO ₂	DMF	26 ^c
	(100mg)		
2	BiCl ₃ -SiO ₂	DMF:MeOH(4:1)	33
	(100mg)		,
3	SbCl ₃ -SiO ₂	DMF	Trace ^a
	(100mg)		
4	SbCl ₃ -SiO ₂	DMF:MeOH(4:1)	29
-	(100mg)		<i>(</i> 2
5	$Ln(OIf)_3-SiO_2$	DMF	63
	(100mg)		(a)
6	$Ln(OIT)_3-SiO_2$	$DMF:H_2O(4:1)$	68
7	(100mg)		50
/	$Ln(OII)_3-SiO_2$	DMF:1-PrOH(4:1)	59
0	(100 mg) L $n(\text{OTf})$ SiO	$DME \cdot M_{2}OH(4, 1)$	70
0	(100 mg)	DMI ¹ .MeOII(4.1)	19
0	(100mg) L n(OTf)a-SiOa	$DME M = OH(4 \cdot 1)$	81
,	(150 mg)	Divit Webri(4.1)	01
10	Ln(OTf)a-SiOa	$DMF \cdot MeOH(4 \cdot 1)$	88
10	(200mg)	2	
11	Ln(OTf) ₃ -SiO ₂	DMF:MeOH(4:1)	85
	(250mg)		

^a The reaction between 1a and sodium azide (2 equiv) was performed in the presence of the various catalysts in 5mL solvent at 100°C for 12h.

^b Isolated yield.

^{c&d} Silica supported BiCl₃ and SbCl₃ were prepared by impregnating respective catalyst (0.5mmol) on 1g silica gel (200-300 mesh).

The solvent has profound influence on the product yields. The synergy of the combination of DMF and MeOH in the ratio 4:1 drives the transformation effortlessly to yield 88% of 5-phenyl-*1H* tetrazole at 100°C (Table1). To study the varying effect of the temperature, the reaction was initially carried out at room temperature and then elevated to 80 °C, 100°C and 120 °C respectively. It was explicit from Table 2 that yield of the reaction was considerably enhanced at 100 °C. The yield remains almost constant at further elevated temperature.

Table 2. Effect of temperature on the formation of 3a from 1a^a

Entry	1	2	3	4
Temperature	Room temperature	80 ⁰ C	100 ⁰ C	120 ⁰ C
Yield ^b		56	88	86

 a The reaction between 1a and sodium azide (2 equiv) was performed in the presence of Ln(OTf)_3-SiO_2(200mg) in DMF:MeOH (5mL, 4:1) for 12h.

^b Isolated yield.

Significance of heterogeneous catalyst over the homogeneous counterpart is its ease of separation and reusability without loss of activity. In relevance with this, we successfully achieved the recovery of catalyst from reaction mixture by simple filtration and the solid residue obtained was subjected to centrifugal washing with ethanol (2x15mL) by drying in an oven at 100 °C for 3-4 hours. This assisted in keeping the catalyst surface active. It is noteworthy, that the recycled catalyst retained optimum activity until 4th cycle after which a drop in yield was observed.

Table 3. Reusability of $Ln(OTf)_3$ -SiO₂in the synthesis of **3a** from $1a^a$

Run	1 st	2 nd	3 rd	4 th	5 th
Yield ^b	88	85	82	78	62

 a The reaction between 1a and sodium azide (2 equiv.) was performed in the presence of Ln(OTf)_3-SiO_2 (200mg) in DMF:MeOH (5mL, 4:1) at 100 $^{\rm 0}C$.

^b Isolated yield.

We investigated the substrate scope and generality of the protocol by employing structurally divergent benzonitriles bearing activating and deactivating groups and few heteroaromatic nitriles. The methodology worked well for most of the aromatic and heteroaromatic nitriles which gave excellent yields over 80% and all the reactions proceeded to completion within 7 to 10 hours. As depicted in Table 2, best percentage conversions were obtained for nitriles with electron withdrawing substituents viz. -NO2, -Cl, -Br as compared to electron donating groups. Hetetroaromatics (entries 10, 11) gave respectably good yields. Not only the nature of the substituent in benzonitrile, but also the position of the substituent is known to affect the reaction yield. Relatively lower yield in case of 2-hydroxy benzonitrile (77%, entry 9) and 2-methyl benzonitrile (74%, entry 5) was obtained in comparison with their para substituted analogues (entries 8, 4). Low yield accompanied with longer reaction time may be attributed to the steric hindrance by the orthosubtituents that hampered the tetrazole formation. The current protocol was however inefficient for benzyl nitrile and other aliphatic nitriles.

Table 2. $Ln(OTf)_3$ -SiO2 promoted synthesis of 5-substitutedtetrazoles**3a-31**





The reaction between various nitriles (1a-11) and sodium azide (2 equiv.) was performed in the presence of $Ln(OTf)_3$ -SiO₂ (200mg) in DMF:MeOH (5mL, 4:1) at 100⁰C.

^b Isolated yield.

Sharpless et al. have reported previously in the study of azidenitrile cycloaddition catalyzed by Zn^{2+} , that co-ordination of the nitrile substrate to the Lewis acidic zinc is the source of the catalysis in the formation of *1H* tetrazoles which is supported by model calculations using density functional theory and corroborated with experimental rate studies.³¹ In our case, we suspect similar kind of interaction between Lewis acidic Ln³+ and nitriles which might promote [3+2] cycloaddition to render 5-substituted tetrazoles in excellent yields.

In conclusion, we report a facile and atom economical synthesis of 5 substituted 1H tetrazoles from various aromatic/ heteroaromatic nitriles and sodium azide with $Ln(OTf)_3$ - SiO₂ as an effective heterogeneous catalyst. This present protocol serves the purpose of completing the cycloaddition process in shorter time, eliminating the hazards of direct use of hydrazoic azid, enhancement of yield, separation and reusability of the catalyst for four subsequent cycles with appreciably high yields. This straightforward and simple procedure may supersede most of the conventional procedures involving homogeneous catalytic systems and find widespread application into organic synthesis for preparing tetrazoles.

Preparation of Ln(OTf)₃- SiO₂ catalyst

To a solution of $Ln(OTf)_3$ (0.5mmol) in EtOH (10mL) was added silica gel (1g, 200-300 mesh) and stirred at room temperature for 4-5 hours. The solvent was evaporated under reduced pressure rendering a white free flowing powder. It was kept under vacuum at room temperature.

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- 30. Typical procedure for the synthesis of 5-phenyl-1Htetrazole

A mixture of benzonitrile (1mmol), sodium azide (2mmol), Ln(OTf)₃- SiO₂ (200mg) and DMF: MeOH (4:1, 5mL) in a pressure vial was initially stirred at room temperature. After 30 min, the temperature of the reaction mixture was raised to 100 °C and stirred for another 7 hours. After consumption of **1a** (as indicated by TLC), the catalyst was separated by filtration and the filtrate was treated with ethyl acetate (15mL). The organic layer was washed with 4N HCl (20mL). The resultant organic layer was separated and the aqueous layer was extracted with ethyl acetate (15mL). The combined organic layer was washed with water (2 x 10mL), dried over anhydrous sodium sulphate and concentrated to afford white crystalline solid. *5-phenyl-1H tetrazole(3a)*

IR (KBr, cm-1): 3331, 2907, 2850, 2611, 1607, 1485, 1433, 1050, 828, 742. ¹H NMR (300 MHz, CDCl3): 8.04 8.007 (m, 1H), 7.611- 7.574 (m, 2H). ¹³C NMR (75 MHz, CDCl3): 156.03, 131.19, 129.08, 126.805, 123.924. MS: m/z = 146 [M]+.

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Scheme 1: Synthesis of 5-substitued tetrazoles via [3+2] cycloaddition between nitriles and sodium azide

Entry	Catalyst	Solvent (ratio)	Yield ^b (%)	
1	BiCl ₃ -SiO ₂	DMF	26 ^c	
	(100mg)			
2	BiCl ₃ -SiO ₂	DMF:MeOH(4:1)	33	
	(100mg)			
3	SbCl ₃ -SiO ₂	DMF	Trace ^d	
	(100mg)			
4	SbCl ₃ -SiO ₂	DMF:MeOH(4:1)	29	
	(100mg)			
5	$Ln(OTf)_3$ -SiO ₂	DMF	63	
	(100mg)			
6	$Ln(OTf)_3$ -SiO ₂	$DMF:H_2O(4:1)$	68	
	(100mg)			
7	$Ln(OTf)_3$ -SiO ₂	DMF: i-PrOH(4:1)	59	
	(100mg)			
8	$Ln(OTf)_3$ -SiO ₂	DMF:MeOH(4:1)	79	
	(100mg)			
9	$Ln(OTf)_3$ -SiO ₂	DMF:MeOH(4:1)	81	
	(150mg)			
10	Ln(OTf) ₃ -SiO ₂	DMF:MeOH(4:1)	88	
	(200mg)			
11	Ln(OTf) ₃ -SiO ₂	DMF:MeOH(4:1)	85	
	(250mg)			

Table1.Effect of various reaction parameters on the formation of tetrazoles 3a from 1a^a

^a The reaction between 1a and sodium azide (2 equiv) was performed in the presence of the various catalysts in 5mL solvent at 100°C for 12h.

^b Isolated yield.

^{c&d} Silica supported BiCl₃ and SbCl₃ were prepared by impregnating respective catalyst (0.5mmol) on 1g silica gel (200-300 mesh).

Table2. Effect of	temperature on	the formation	of 3a from	1a'

Entry	1	2	3	4
Temperature	Room temperature	80 ⁰ C	100°C	120 ⁰ C
Yield ^b		56	88	86

^a The reaction between 1a and sodium azide (2 equiv) was performed in the presence of Ln(OTf)₃-SiO₂(200mg) in DMF:MeOH (5mL, 4:1) for 12h.

^b Isolated yield.

Table3. Reusability of Ln(OTf)₃-SiO₂in the synthesis of 3a from 1a^a

Run	1 st	2 nd	3 rd	4 th	5 th
Yield ^b	88	85	82	78	62

^a The reaction between 1a and sodium azide (2 equiv) was performed in the presence of $Ln(OTf)_3$ -SiO₂ (200mg) in DMF:MeOH (5mL, 4:1) at 100^oC.

^b Isolated yield.

Table4.Ln(OTf)₃-SiO₂ promoted synthesis of 5-substituted tetrazoles 3a-31





The reaction between various nitriles (1a-11) and sodium azide (2 equiv.) was performed in the presence of $Ln(OTf)_3$ -SiO₂ (200mg) in DMF:MeOH (5mL, 4:1) at 100^oC.

^b Isolated yield.